TABLE 8.6.2A. NUMBER (%)[a] OF PATIENTS WITH TEAEs OCCURRING IN > 5% OF THE PATIENTS IN A TREATMENT GROUP, EXCLUDING INFECTION AND MALIGNANCY: INDIVIDUAL STUDIES 301 AND 302

Body System Adverse Event	Rapamune 2 mg/day (n = 281)[b] (n = 218)[c]	Rapamune 5 mg/day (n = 269)[b] (n = 208)[c]	Azathioprine (n = 160)[b]	Placebo (n = 124)[c]
Chills				
Study 301	24 (9)	28 (10)	8 (5)	
Study 302	14 (6)[f]	32 (15)		13 (10)
Cushing's Syndrome				
Study 301	21 (7)[d]	24 (9)[d]	2 (1)	
Study 302	17 (8)	17 (8)		15 (12)
Diarrhea				
Study 301	90 (32)[f]	112 (42)[d]	44 (28)	
Study 302	54 (25)	72 (35)		33 (27)
Dysuria				
Study 301	26 (9)	40 (15)	22 (14)	
Study 302	23 (11)[f]	38 (18)[e]		11 (9)
Ecchymosis				
Study 301	18 (6)	26 (10)	13 (8)	
Study 302	16 (7)[f]	29 (14)[e]		8 (6)
Edema				
Study 301	68 (24)[f]	43 (16)	37 (23)	
Study 302	44 (20)	38 (18)		18 (15)
Epistaxis				
Study 301	10 (4)	18 (7)[d]	1 (1)	
Study 302	16 (7)[e]	25 (12)[e]		2 (2)
Face Edema				
Study 301	17 (6)[f]	37 (14)[d]	9 (6)	
Study 302	13 (6)[f]	26 (13)		7 (6)
Fever				
Study 301	76 (27)	90 (33)	52 (33)	
Study 302	51 (23)[f,e]	71 (34)		44 (35)
Hirsutism				
Study 301	17 (6)[f]	37 (14)[d]	5 (3)	
Study 302	19 (9)	19 (9)		11 (9)
Hypercalcemia				
Study 301	10 (4)[d]	5 (2)[d]	14 (9)	
Study 302	9 (4)	5 (2)		3 (2)
Hypercholesterolemia				
Study 301	108 (38)	113 (42)	53 (33)	
Study 302	94 (43)[e]	96 (46)[e]		28 (23)
Hyperkalemia				
Study 301	42 (15)[d]	32 (12)[d]	38 (24)	
Study 302	38 (17)	29 (14)[e]		33 (27)
Hyperlipemia				
Study 301	106 (38)[d]	118 (44)[d]	45 (28)	
Study 302	98 (45)[f,e]	118 (57)[e]		28 (23)

TABLE 8.6.2A. NUMBER (%)[a] OF PATIENTS WITH TEAEs OCCURRING IN > 5% OF THE PATIENTS IN A TREATMENT GROUP, EXCLUDING INFECTION AND MALIGNANCY: INDIVIDUAL STUDIES 301 AND 302

Body System Adverse Event	Rapamune 2 mg/day (n = 281)[b] (n = 218)[c]	Rapamune 5 mg/day (n = 269)[b] (n = 208)[c]	Azathioprine (n = 160)[b]	Placebo (n = 124)[c]
Hypertension				
Study 301	122 (43)[d]	104 (39)[d]	46 (29)	
Study 302	97 (45)	101 (49)		59 (48)
Hypokalemia				
Study 301	47 (17)	56 (21)[d]	18 (11)	
Study 302	23 (11)[f]	36 (17)[e]		11 (9)
Hypotension				
Study 301	16 (6)[f,d]	30 (11)	24 (15)	
Study 302	12 (6)	18 (9)		10 (8)
Insomnia				
Study 301	38 (14)[f]	58 (22)	28 (18)	
Study 302	29 (13)	29 (14)		10 (8)
LDH Increased				
Study 301	31 (11)	37 (14)	13 (8)	
Study 302	26 (12)[f]	41 (20)[e]		8 (6)
Leukopenia				
Study 301	25 (9)[f,d]	41 (15)	32 (20)	
Study 302	20 (9)	26 (13)		10 (8)
Lymphocele				
Study 301	38 (14)[d]	50 (19)[d]	8 (5)	
Study 302	24 (11)	33 (16)[e]		7 (6)
Rash				
Study 301	35 (12)[d]	34 (13)[d]	9 (6)	
Study 302	22 (10)[f]	41 (20)[e]		8 (6)
Scrotal Edema				
Study 301	18 (6)[d]	15 (6)[d]	2 (1)	
Study 302	4 (2)	10 (5)		2 (2)
Tachycardia				
Study 301	35 (12)[d]	46 (16)[d]	8 (5)	
Study 302	25 (11)[e]	28 (13)[e]		6 (5)
Thrombocytopenia				
Study 301	36 (13)[f]	53 (20)[d]	15 (9)	
Study 302	30 (14)[f]	62 (30)[e]		11 (9)
Thrombotic Thrombocytopenic Purpura				
Study 301	4 (1)	8 (3)	3 (2)	
Study 302	6 (3)[f]	18 (9)		4 (3)

TABLE 8.6.2A. NUMBER (%)[a] OF PATIENTS WITH TEAEs OCCURRING IN > 5% OF THE PATIENTS IN A TREATMENT GROUP, EXCLUDING INFECTION AND MALIGNANCY: INDIVIDUAL STUDIES 301 AND 302

Body System Adverse Event	Rapamune 2 mg/day (n = 281)[b] (n = 218)[c]	Rapamune 5 mg/day (n = 269)[b] (n = 208)[c]	Azathioprine (n = 160)[b]	Placebo (n = 124)[c]
Upper Respiratory Infection				
Study 301	57 (20)[d]	64 (24)[d]	20 (13)	
Study 302	57 (26)	48 (23)		29 (23)

a: The percent is based on the total number of patients in the treatment group.
b: The total number of patients in each treatment group; study 301.
c: The total number of patients in each treatment group; study 302.
d: Pairwise comparison significant for 2 mg/day or 5 mg/day Rapamune versus azathioprine.
e: Pairwise comparison significant for 2 mg/day or 5 mg/day Rapamune versus placebo.
f: Pairwise comparison significant for 2 mg/day Rapamune versus 5 mg/day Rapamune.

8.6.3 TEAEs Related to Infection

8.6.3.1 Overview

Rates of infection are of particular interest in transplant patients, as their frequency reflects the degree of immunosuppression in this population. All of the analyses for infections were done on an intent-to-treat basis using protocol-specified guidelines to document the occurrence of infections.

This section reviews the one-year incidence of clinically important infections in the phase 3 Rapamune trials. The rates of infection are compared to those seen in two previously published studies: the tricontinental mycophenolate mofetil (MMF) trial[38] and the tacrolimus renal trial.[6] The design of the tricontinental MMF trial was similar to Rapamune study 301; it was blinded, compared the efficacy and safety of 2 doses of MMF to azathioprine, and antibody induction therapy was not permitted. The tacrolimus renal trial was open label and compared the efficacy and safety of tacrolimus to CsA in patients concomitantly receiving corticosteroids, azathioprine, and antilymphocyte antibody induction therapy.

8.6.3.2 Opportunistic Infections

As shown in Table 8.6.3.2A, there was no increase in the incidence of opportunistic infection in either Rapamune treatment group compared to the control groups, except for a higher incidence of mucosal *Herpes simplex* infection in the Rapamune 5 mg/day group. The rate is numerically higher in study 301 (10.2%), and in study 302 the difference among the groups for mucosal *Herpes simplex* is significant (the rate is highest in the Rapamune 5 mg/day group, 19.2%). However, these rates are

lower than those reported in the MMF trial (21% to 25%; Table 8.6.3.2B). All cases of PCP and all but one case of mycobacterial infection occurred in patients in the 301 study.

TABLE 8.6.3.2A. RATE OF OPPORTUNISTIC INFECTIONS (PERCENTAGES): 12- MONTH DATA, STUDIES 301 AND 302

	Rapamune 2 mg/day		Rapamune 5 mg/day		Azathioprine	Placebo
Opportunistic Infection	301 (n = 284)	302 (n = 227)	301 (n = 274)	302 (n = 219)	301 (n = 161)	302 (n = 130)
CMV[a] (generalized)	3.2	4.8	2.9	7.8	5.6	5.4
CMV (tissue-invasive)	0.7	0.9	1.1	0.9	1.2	0.8
Herpes zoster	3.2	3.5	4.4	4.6	5.0	3.8
Herpes simplex	4.6	8.8	10.2	19.2[b]	4.4	6.9
Epstein-Barr virus	0	1.3	0.4	0.9	0	0.8
PCP[c]	0.7	0	0.4	0	0	0
Mycobacterial[d]	1.8	0.4	1.1	0	0.6	0

a: Cytomegalovirus.
b: In study 302, the difference among the groups for *Herpes simplex* is statistically significant based on examination of confidence intervals (CI = 5.5 - 13.3 for Rapamune 2 mg/day; 14.2 - 25.0 for Rapamune 5 mg/day; and 3.2 - 12.7 for placebo).
c: Pneumocystis carinii pneumonia.
d: Includes pulmonary and extrapulmonary infections, including patients who had infections in the second year.

Table 8.6.3.2B summarizes the rates of opportunistic infections in the tricontinental MMF trial, the tacrolimus trial, and the Rapamune phase 3 trials.

TABLE 8.6.3.2B. RATES OF OPPORTUNISTIC INFECTIONS (PERCENTAGES)

	Infection					
Trial (Length of Follow-Up) / Treatment Groups	CMV[a]	CMV[b]	PCP[c]	*Herpes simplex*	*Herpes zoster*	Mycobacterial
MMF Tricontinental (≥ 1 y)						
MMF 3 g (n = 164)	11	11	0	25	8	nd[d]
MMF 2 g (n = 171)	12	7	0	21	7	nd
Azathioprine (n = 162)	12	6	2.0	24	7	nd
Tacrolimus Renal (up to 1 y)						
Tacrolimus (n = 205)	10.2	9.3	0	7.3	0	0
CsA (n = 207)	12.6	6.8	0	6.3	1.0	1.0
Rapamune 301 and 302 (≤ 1 y)						
Rapamune 2 mg/d (n = 511)						
Study 301 (n = 284)	3.2	0.7	0.7	4.6	3.2	1.8
Study 302 (n = 227)	4.8	0.7	0	8.8	3.5	0.4
Rapamune 5 mg/d (n = 493)						
Study 301 (n = 274)	2.9	1.1	0.4	10.2	4.4	1.1
Study 302 (n = 219)	7.8	0.9	0	19.2	4.6	0
Placebo (n = 130)	5.4	0.8	0	6.9	3.8	0
Azathioprine (n = 161)	5.7	1.2	0	4.4	5.0	0.6

a: Generalized cytomegalovirus infection.
b: Tissue-invasive cytomegalovirus infection.
c: *Pneumocystis carinii* pneumonia.
d: nd, not discussed.

In the Rapamune trials, the rates of CMV infection, especially tissue-invasive CMV, were lower in all groups, compared to the rates in the MMF and tacrolimus trials. This may be explained partly by adherence to the CMV prophylaxis, which was protocol mandated in all CMV-negative recipients of allografts from CMV-positive donors and recommended for all other patients. The majority of patients in the Rapamune trials did receive CMV prophylaxis. The rate of CMV prophylaxis in the MMF and tacrolimus trials is not specified.

Based on these results, CMV prophylaxis will be recommended for 3 months after transplantation in Rapamune-treated patients, particularly for patients at increased risk for CMV disease.

In addition, PCP prophylaxis will be recommended for one year following transplantation for patients receiving Rapamune. This recommendation is based on the favorable results seen in the phase 3 trials, in which PCP prophylaxis was protocol mandated for one year. Only 3 cases of PCP were reported; none of these patients were receiving prophylaxis at the time of the diagnosis. By contrast, in the Rapamune phase 2 dose ranging study (203), where PCP prophylaxis was recommended but not required, PCP was reported in 9 of 187 patients, 2 of whom died from the

disease. Again, none of these patients were receiving prophylaxis at the time of the diagnosis. One of the patients was diagnosed on day 178 of Rapamune therapy and another on day 257, suggesting that prophylaxis should be recommended for up to one year.

Ten (10) cases of mycobacterial infection were reported (4 with extra-pulmonary manifestations), including one documented case of *Mycobacterium avium-intracellulare* in a patient in the azathioprine group. The other 9 cases (including one case of *Mycobacterium haemophilum*) occurred in patients in the Rapamune cohorts. Four (4) of these patients had been off Rapamune therapy for at least 50 days. All patients with tuberculosis responded to therapy except one patient who died from disseminated tuberculosis. This patient had discontinued study drug (Rapamune 2 mg/day) 71 days before the diagnosis. The rates of mycobacterial infection in the Rapamune groups (0.6% to 1.2%) were similar to that reported for the CsA control group in the tacrolimus renal trial (1.0%).[2]

8.6.3.3 Other Clinically Important Infections

Table 8.6.3.3A shows the rate of sepsis, pyelonephritis, wound infection, and pneumonia across treatment groups. None of these events were statistically significantly different when analyzed by study.

TABLE 8.6.3.3A. RATES OF CLINICALLY IMPORTANT INFECTIONS: 12-MONTH DATA, STUDIES 301 AND 302[a]

	Rapamune 2 mg/day		Rapamune 5 mg/day		Azathioprine	Placebo
Opportunistic Infection	301 n = 284	302 n = 227	301 n = 274	302 n = 219	301 n = 161	302 n = 130
Sepsis	8.5	5.3	8.0	8.2	3.7	6.9
Pyelonephritis / UTI[a]	19.1	26.2	22.1	32.0	28.5	23.8
Wound infections	6.0	8.8	8.8	11.0	5.0	8.5
Pneumonia	6.0	4.8	7.7	7.3	3.1	6.9

a: Urinary tract infection.

Table 8.6.3.3B tabulates all cases of pneumonia, including patients with PCP, CMV, mycobacterial, bacterial, and fungal pneumonia. None of these events were statistically significantly different when analyzed by study.

TABLE 8.6.3.3B. ETIOLOGY OF PNEUMONIA (n, %): STUDIES 301 AND 302, 12-MONTH DATA

	Rapamune 2 mg/day		Rapamune 5 mg/day		Azathioprine	Placebo
Pneumonia	301 (n = 284)	302 (n = 227)	301 (n = 274)	302 (n = 219)	301 (n = 161)	302 (n = 130)
PCP	2 (0.7)	0	1 (0.4)	0	0	0
CMV	0	1 (0.4)	2 (0.7)	1 (0.5)	0	2 (1.5)
Viral (non-CMV)	0	0	1 (0.4)	0	0	0
Mycobacterial	5 (1.8)	0	1 (0.4)	0	1 (0.6)	0
Bacterial	2 (0.7)	1 (0.4)	7 (2.6)	5 (2.3)	2 (1.2)	5 (3.8)
Fungal	1 (0.4)	1 (0.4)	2 (0.7)	3 (1.4)	0	1 (0.8)
Organism unspecified	7 (2.5)	8 (3.5)	7 (2.6)	7 (3.2)	2 (1.2)	1 (0.8)
Total	17 (6.0)	11 (4.8)	21 (7.7)	16 (7.3)	5 (3.1)	9 (6.9)

8.6.3.4 Conclusions

- Treatment of renal transplant recipients with Rapamune 2 mg/day or 5 mg/day in combination with CsA and corticosteroids does not result in added risk of infection compared with control groups. This is demonstrated by the fact that, with the exception of Herpes simplex, the rates of opportunistic and other clinically important infections were comparable among treatment groups.

- Rates of various opportunistic infections in Rapamune trials are similar to or lower than those reported in trials of other immunosuppressive agents.

8.6.4 Deaths

There were no significant differences in the overall death rate by treatment group by study at 12 months. The rates ranged from 1.9% in the azathioprine group (study 301) to 5.4% in the placebo group (study 302). In the cumulative data, the death rates ranged from 3.1% in the azathioprine group to 6.9% in the placebo group. Infections and vascular events (cardiovascular and cerebrovascular) were the most common cause of death in all groups. Deaths from malignancies occurred at both doses of Rapamune as well as in the azathioprine and placebo groups. Table 8.6.4A presents information on the cause of death by study.

TABLE 8.6.4A. CAUSES OF DEATH BY STUDY

Cause of Death	Rapamune 2 mg/day 301 (n = 284)	Rapamune 2 mg/day 302 (n = 227)	Rapamune 5 mg/day 301 (n = 274)	Rapamune 5 mg/day 302 (n = 219)	Azathioprine 301 (n = 161)	Placebo 302 (n = 130)
0-12 Months						
Vascular	3 (1.1)	3 (1.3)	6 (2.2)	2 (0.9)	1 (0.6)	4 (3.1)
Infection	3 (1.1)	4 (1.8)	2 (0.7)	4 (1.8)	1 (0.6)	1 (0.8)
Malignancy	1 (0.4)	0	0	2 (0.9)	1 (0.6)	0
Other	1 (0.4)	1 (0.4)	3 (1.1)	3 (1.4)	0	2 (1.5)
Total	8 (2.8)	8 (3.5)	11 (4.0)	11 (3.8)	3 (1.9)	7 (5.4)
Cumulative						
Vascular	5 (1.8)	4 (1.8)	7 (2.6)	2 (0.9)	3 (1.9)	5 (3.8)
Infection	5 (1.8)	6 (2.6)	2 (0.7)	4 (1.8)	1 (0.6)	1 (0.8)
Malignancy	1 (0.4)	2 (0.8)	0	2 (0.9)	1 (0.6)	1 (0.8)
Other	3 (1.1)	1 (0.4)	3 (1.1)	3 (1.4)	0	2 (1.5)
Total	14 (4.9)	13 (5.7)	12 (4.4)	11 (3.8)	5 (3.1)	9 (6.9)

8.6.5 Graft Loss

Table 8.6.5A presents information regarding the etiology of graft loss. The most common etiology of all graft loss was death with a functioning graft; the second most common was acute rejection. At 12 months, the incidence of graft loss did not differ among treatment groups in either study. The rate of graft loss ranged from 5.6% in the Rapamune 2 mg/day group (study 301) and the azathioprine group to 12.3% in the placebo group.

In the cumulative data, the most common etiology for graft loss remained death with a functioning graft, and the second most common in all but the placebo group was acute rejection. The rate of graft loss ranged from 6.8% in the azathioprine group to 13.8% in the placebo group.

TABLE 8.6.5A. ETIOLOGY OF GRAFT LOSS FOLLOWING TRANSPLANTATION: NUMBER (%) OF PATIENTS (STUDIES 301 AND 302)

	Rapamune 2 mg/day		Rapamune 5 mg/day		Azathioprine	Placebo
Etiology of Graft Loss	301 (n=284)	302 (n=227)	301 (n=274)	302 (n=219)	301 (n=161)	302 (n=130)
0 - 12 Months						
Death with functioning graft	7 (2.5)	8 (3.5)	8 (2.9)	9 (4.1)	2 (1.2)	6 (4.6)
Acute rejection	1 (0.4)	6 (2.6)	6 (2.2)	2 (0.9)	3 (1.9)	2 (1.5)
Acute tubular necrosis	1 (0.4)	4 (1.8)	2 (0.7)	2 (0.9)	3 (1.9)	4 (3.0)
Renal vein or artery thrombosis	2 (0.7)	2 (0.8)	1 (0.4)	2 (0.9)	1 (0.6)	2 (1.5)
Other	5 (1.8)	3 (1.3)	3 (1.1)	5 (2.3)	0	2 (1.5)
Total	16 (5.6)	23 (10.1)	20 (7.3)	20 (9.1)	9 (5.6)	16 (12.3)
Cumulative						
Death with functioning graft	13 (4.6)	13 (5.7)	9 (3.3)	9 (4.1)	4 (2.5)	8 (6.2)
Acute rejection	2 (0.7)	6 (2.6)	6 (2.2)	2 (0.9)	3 (1.9)	2 (1.5)
Acute tubular necrosis	1 (0.4)	4 (1.8)	2 (0.7)	2 (0.9)	3 (1.9)	4 (3.0)
Renal vein or artery thrombosis	2 (0.7)	2 (0.8)	1 (0.4)	2 (0.9)	1 (0.6)	2 (1.5)
Other	7 (2.5)	3 (1.3)	3 (1.1)	5 (2.3)	0	2 (1.5)
Total	25 (8.8)	28 (12.3)	21 (7.7)	20 (9.1)	11 (6.8)	18 (13.8)

8.6.6 Malignancy

Similar to infection, rates of malignancy are of particular interest in transplant patients because their frequency also reflects the degree of immunosuppression in this population. This section reviews the one-year incidence of clinically important malignancy in the phase III Rapamune trials. The rates of malignancy are compared to those in the tricontinental mycophenolate mofetil (MMF) trial[38] and the tacrolimus renal trial.[6] In this analysis, PTLD and lymphoma are combined under the same heading (PTLD/lymphoma).

As shown in Table 8.6.6A, the incidence of malignancy during the first year after transplantation was comparable across treatment groups, except for a higher incidence of PTLD/lymphoma in patients in the Rapamune 5 mg/day group (difference not significant among treatment groups). The rates of PTLD are similar to what has been reported in trials of other immunosuppressive agents (0.6% to 2.4%).[6,38]

In study 301 (data not shown), the rates of PTLD at 12 months were 0.4%, 0.7%, and 0.6% in the Rapamune 2 mg/day, Rapamune 5 mg/day, and azathioprine, groups, respectively; in study 302, the rates of PTLD were 0.4%, 2.3%, and 0 in the Rapamune 2 mg/day, Rapamune 5 mg/day, and placebo groups, respectively. The differences among groups were not statistically significant in either study. The numerically higher rate of PTLD in the Rapamune 5 mg/day group in the combined

data (see Table 8.6.6A) was due mainly to the higher rate of PTLD in the Rapamune 5 mg/day group in study 302.

TABLE 8.6.6A. INCIDENCE OF MALIGNANCY
(STUDIES 301 AND 302 COMBINED, 12 MONTHS)

Malignancy	Rapamune 2 mg/day (n = 511)	Rapamune 5 mg/day (n = 493)	Placebo (n = 130)	Azathioprine (n = 161)
PTLD[a,b]	0.4%	1.4%	0	0.6%
Skin (excluding melanoma)[c]	0.4%	1.4%	3.1%	1.2%
Other	0.6%	0.6%	0	0

a: Post-transplant lymphoproliferative disorder.
b: $p > 0.05$ across treatment groups.
c: $p < 0.05$, placebo vs Rapamune 2 mg/day.

The frequency of PTLD from the cumulative data base (all patients followed for at least 1 year, with some followed up to 2 years; data not shown) reveals rates of 1.0%, 2.0%, 0.8% and 0.6% in the Rapamune 2- and 5 mg/day, placebo, and azathioprine groups, respectively. These rates, again, remain within the range of previously reported incidences of PTLD in patients treated with other immunosuppressive agents.

8.6.7 Thrombotic Events in Renal Transplant Recipients

Review of the phase III data revealed 6 categories of vascular thrombosis: transplant thrombosis, deep vein thrombosis, thrombosis of arteriovenous fistulas, superficial venous thrombosis, arterial thrombosis, and thrombosis of unidentified vessels. The rates of all thrombotic events among treatment groups were: 7.2%, 7.3%, 7.7%, and 5.0% in the Rapamune 2 mg/day, Rapamune 5 mg/day, placebo and azathioprine groups, respectively. There was no statistically significant difference among treatment groups in the total crude rate or in any of the 6 categories defined.

8.6.8 Post-Transplant Diabetes Mellitus

The patients in studies 301 and 302 were analyzed for posttransplant diabetes mellitus (PTDM). The definition of PTDM used for this analysis was that of Mayer, et al,[39] in which patients were said to have PTDM if they: 1) had no history of insulin- or non-insulin dependent diabetes before transplantation and 2) required insulin after transplantation for 30 or more consecutive days, with fewer than 5 days of interruption, to maintain a normal, fasting blood glucose level.

Twenty seven (27) patients met these criteria. The rates of insulin use for 30 or more consecutive days were 0% in the placebo group, 2.0% in the azathioprine group, 3.0% in the combined Rapamune 2 mg/day groups, and 4.6% in the combined Rapamune 5 mg/day groups. The rate of insulin use in blacks exceeded that in non-blacks. There were no significant differences in the rates of PTDM among groups for all patients, blacks, males, or females. The rates of insulin use for 30 or more consecutive days in the Rapamune trials are comparable to the rates of 2.2% and 4.0% reported for CsA-treated patients in the European and U.S. multicenter tacrolimus trials, respectively,[6] and lower than the rates reported for the tacrolimus arms (8.3% and 19.9%, respectively).

8.7 Clinical Laboratory Evaluation

8.7.1 Liver Function Tests

Table 8.7.1A shows the incidence of on-therapy liver enzyme elevations for the first year of the phase III trials, combining the results from both trials. Alkaline phosphatase elevations greater than 5 normal were very rare. No patients had alkaline phosphatase elevations greater than 10 times normal. Elevations of 5 or 10 times normal for SGOT (AST) and SGPT (ALT) were also uncommon. There was no significant difference among treatment groups for these elevations.

TABLE 8.7.1A. NUMBER (%) OF PATIENTS WITH LIVER FUNCTION TESTS ≥ 5 AND ≥10 TIMES NORMAL (STUDIES 301 AND 302)

Test, ≥ Times Normal	Rapamune 2 mg/day (n = 497)	Rapamune 5 mg/day (n = 471)	Placebo (n = 124)	Azathioprine (n = 157)
Alkaline phosphatase ≥ 5	1 (< 1.0)	2 (< 1.0)	1 (< 1.0)	0
AST ≥ 5	12 (2.4)	11 (2.3)	2 (1.6)	4 (2.5)
AST ≥ 10	3 (< 1.0)	1 (< 1.0)	0	0
ALT ≥ 5	19 (3.8)	25 (5.3)	8 (6.5)	3 (1.9)
ALT ≥ 10	7 (1.4)	2 (< 1.0)	2 (1.6)	0

8.7.2 Renal Function

The effect of Rapamune on renal function has been extensively investigated. The preclinical and phase 2 data summarized below demonstrate that Rapamune lacks intrinsic nephrotoxicity. In phase 3 studies, the creatinine levels over time were higher in the Rapamune-treated patients compared with the azathioprine and placebo cohorts. An enhancement of CsA nephrotoxicity may be the likely explanation, and a reduction of CsA doses may have ameliorated this effect. Preliminary data from CsA-withdrawal studies in progress support this hypothesis.

Constraints within the double-blind design of the phase 3 trials prevented the investigators from substantially decreasing the CsA dose when CsA toxicity was suspected: 1) CsA trough concentrations were protocol mandated, which did not allow the investigators to reduce the CsA doses, as they might have done in clinical practice; 2) The investigators tended to maintain the CsA concentrations within the upper range of the target concentration for all patients to maximize immunosuppression because they were blinded to the study drug assignments.

8.7.2.1 Background and Preclinical Summary

Studies in various animal models have confirmed the lack of intrinsic nephrotoxicity of Rapamune.[40] Andoh et al,[41] using a salt-depleted model of the Sprague-Dawley rats, showed that two-week exposure to CsA or tacrolimus led to a significant decline in GFR compared with control animals (1.1 vs 0.2 cc/min/100g). This decline in GFR was associated with a marked decrease in the urinary excretion of nitric oxide metabolites (Table 8.7.2.1A). Rapamune-treated animals showed no such decrement in GFR (1.1 vs 1.0 cc/min/100g) or decline in nitric oxide excretion.

TABLE 8.7.2.1A. CHANGE IN GFR, RBF, AND URINARY EXCRETION OF NITRIC OXIDE AT DAY 14[a]

	Vehicle	CsA	Tacrolimus	Rapamune
GFR[b] (mL/min/100 g)	1.1 ± 0.1	0.2 ± 0.1[e]	0.2 ± 0.1[e]	1.0 ± 0.1
RBF[c] (mL/min/100 g)	3.3 ± 0.2	1.9 ± 0.2[e]	2.0 ± 0.2[e]	3.1 ± 0.3
UNO[d] (µmol/24 hr)	15.2 ± 1.2	9.5 ± 0.6[e]	10.6 ± 0.8[e]	19.4 ± 1.7

a: Table modified from Bennett et al (reference 42).
b: GFR - inulin clearance.
c: RBF - renal blood flow.
d: UNO - urinary excretion of NO_2/NO_3
e: $p < 0.01$ vs vehicle.

It is likely that some or all of the renal toxic effects of CsA and tacrolimus are mediated via inhibition of calcineurin. Rapamune binds and inhibits mammalian Target of Rapamycin (mTOR), a key regulatory kinase, and as a result suppresses not only lymphocyte proliferation but growth factor-mediated proliferation of fibroblasts, endothelial cells, and smooth muscle cells. Rapamune does not inhibit calcineurin and should lack the nephrotoxic potential of CsA and tacrolimus.

8.7.2.2 Rapamune as Primary Therapy

Three (3) phase 2 trials also provide evidence that Rapamune lacks inherent nephrotoxicity. In 2 of these trials (studies 207 and 210), Rapamune was administered without CsA in renal

transplant patients, and in 1 other study (204) Rapamune was administered as monotherapy for patients with psoriasis.

In brief, studies 207 and 210 were randomized open label, parallel group studies in de novo renal transplant patients, using triple therapy with either CsA or Rapamune in combination with steroids and azathioprine (study 207) or MMF (study 210). A total of 161 patients were randomized in both studies. Rapamune dose administration was concentration-controlled with the average maintenance dose being 6 to 9 mg/day. Table 8.7.2.2A shows the mean serum creatinine values at various time intervals for the two treatment groups (studies 207 and 210 combined). The serum creatinine is consistently lower in the Rapamune-treated patients. At one year, the mean on-therapy creatinine value in the Rapamune-treated groups was 116.9 μmol/L (1.32 mg/dL) compared to 138.7 μmol/L (1.57 mg/dL) in the CsA cohort (p = 0.007).

TABLE 8.7.2.2A. ADJUSTED MEAN VALUES ± SEM FOR CREATININE (μmol/L): STUDIES 207 AND 210 COMBINED

Week	Rapamune	CsA	ANOVA
4	190.0 ± 18.4[a] [2.15 ± 0.21][b] (67)[c]	177.1 ± 13.1 [2.00 ± 0.15] (64)	0.572
12	132.4 ± 6.3 [1.50 ± 0.07] (56)	154.0 ± 7.1 [1.74 ± 0.08] (60)	0.026
24	128.4 ± 6.5 [1.45 ± 0.07] (49)	142.0 ± 5.1 [1.61 ± 0.06] (53)	0.101
36	134.1 ± 8.3 [1.52 ± 0.90] (48)	140.0 ± 5.5 [1.58 ± 0.06] (53)	0.542
52	116.9 ± 4.9 [1.32 ± 0.06] (35)	138.7 ± 5.5 [1.57 ± 0.06] (52)	0.007
76	110.5 ± 5.4 [1.25 ± 0.06] (16)	130.6 ± 8.5 [1.48 ± 0.10] (26)	0.091

a: Standard error of the mean.
b: Adjusted mean values ± SEM in mg/dL.
c: Number of patients is shown in parentheses.

In a phase 2 trial of patients with psoriasis (study 204), doses of Rapamune up to 5 mg/m^2 for 12 weeks had no adverse affect on renal function (Table 8.7.2.2B).

TABLE 8.7.2.2B. ADJUSTED MEAN VALUES[a] (± SE) FOR SERUM CREATININE IN RAPAMUNE MONOTHERAPY FOR PSORIASIS (STUDY 204)

	----------Rapamune dose, mg/m²/day---------			Placebo	
Laboratory Test	1 (27)[b]	3 (30)[b]	5 (27)[b]	(30)[b]	ANCOVA
Creatinine (μmol/L)	85.16 ± 1.6	84.42 ± 1.5	85.66 ± 1.6	86.53 ± 1.5	0.795
Creatinine (mg/dL)	0.96 ± 0.02	0.95 ± 0.02	0.97 ± 0.02	0.98 ± 0.02	

a: Adjusted mean value is the mean on-therapy value for a patient with an average baseline.
b: Number in parenthesis indicates the number of pairs used for the adjusted mean.

8.7.2.3 Phase 3 Trials

Table 8.7.2.3A shows the mean on-therapy creatinine values observed in studies 301 and 302 combined. Serum creatinine values are higher in the Rapamune-treated patients over time; however, the serum creatinine level in the Rapamune 2 mg/day group was stable from months 3 to 12. Tables 8.7.2.3B and C show the mean on-therapy creatinine values for studies 301 and 302, respectively. The results from the individual studies were consistent.

TABLE 8.7.2.3A. MEAN VALUES (± SEM) FOR CREATININE (μmol/L): STUDIES 301 AND 302 COMBINED

	---------- Rapamune ----------				
Time	2 mg/day	5 mg/day	Azathioprine	Placebo	ANOVA
Month 1	330.8 ± 11.3[a]	323.6 ± 11.5	350.7 ± 21.6	338.1 ± 25.6	0.704
	[3.74 ± 0.13][b]	[3.66 ± 0.13]	[3.97 ± 0.24]	[3.82 ± 0.29]	
	(496)[c]	(471)	(157)	(124)	
Month 3	155.6 ± 3.2[d,f]	165.0 ± 3.6[d,e]	137.4 ± 6.2	145.1 ± 4.2	< 0.001
	[1.76 ± 0.04]	[1.87 ± 0.04]	[1.55 ± 0.07]	[1.64 ± 0.05]	
	(379)	(349)	(91)	(75)	
Month 6	154.8 ± 3.2[d]	159.7 ± 3.2[d]	129.4 ± 5.5[g]	149.9 ± 7.6	< 0.001
	[1.75 ± 0.04]	[1.81 ± 0.04]	[1.46 ± 0.06]	[1.70 ± 0.09]	
	(323)	(283)	(80)	(66)	
Month 12	158.0 ± 3.2[d,e,f]	171.7 ± 4.3[d,e]	133.1 ± 5.1	136.8 ± 5.4	< 0.001
	[1.79 ± 0.04]	[1.94 ± 0.05]	[1.51 ± 0.06]	[1.55 ± 0.06]	
	(275)	(245)	(78)	(65)	

a: Mean value is the mean on-therapy value. SEM is the standard error of the mean.
b: Adjusted mean values ± SEM in mg/dL.
c: Number of patients.
d: Pairwise significant p-value comparison for a Rapamune treatment group versus azathioprine.
e: Pairwise significant p-value comparison for a Rapamune treatment group versus placebo.
f: Pairwise significant p-value comparison for 2 mg/day Rapamune versus 5 mg/day Rapamune treatment group.
g: Pairwise significant p-value comparison for placebo versus azathioprine treatment group.

TABLE 8.7.2.3B. MEAN VALUES (± SEM) FOR CREATININE (μmol/L) STUDY 301

	Treatment Group			
Time	Rapamune 2 mg/day	Rapamune 5 mg/day	Azathioprine	ANOVA
Month 1	333.7 ± 15.7[a]	295.7 ± 13.8[d]	350.7 ± 21.6	0.063
	[3.77 ± 0.18][b]	[3.35 ± 0.16]	[3.97 ± 0.24]	
	(279)[c]	(265)	(157)	
Month 3	156.9 ± 4.8[d]	160.3 ± 4.8[d]	137.4 ± 6.2	0.022
	[1.77 ± 0.05]	[1.81 ± 0.05]	[1.55 ± 0.07]	
	(213)	(200)	(91)	
Month 6	154.2 ± 3.7[d]	157.6 ± 4.6[d]	129.4 ± 5.5	< 0.001
	[1.74 ± 0.04]	[1.78 ± 0.05]	[1.46 ± 0.06]	
	(177)	(162)	(80)	
Month 12	160.0 ± 4.9[d]	171.1 ± 6.0[d]	133.1 ± 5.1	< 0.001
	[1.81 ± 0.06]	[1.94 ± 0.07]	[1.51 ± 0.06]	
	(139)	(138)	(78)	

a: Mean value is the mean on-therapy value. SEM is the standard error of the mean.
b: Adjusted mean values ± SEM in mg/dL.
c: Number of patients.
d: Pairwise significant p-value comparison for a Rapamune treatment group versus azathioprine.

TABLE 8.7.2.3C. MEAN VALUES (± SEM) FOR CREATININE (μmol/L) STUDY 302

	Treatment Group			ANOVA
Time	Rapamune 2 mg/day	Rapamune 5 mg/day	Placebo	p-Value
Month 1	329.4 ± 16.2[a]	359.5 ± 19.1	338.1 ± 25.6	0.490
	[3.73 ± 0.18][b]	[4.07 ± 0.22]	[3.82 ± 0.29]	
	(218)[c]	(206)	(124)	
Month 3	154.0 ± 4.2	171.3 ± 5.4[d, e]	145.1 ± 4.2	0.002
	[1.74 ± 0.05]	[1.94 ± 0.06]	[1.64 ± 0.05]	
	(166)	(149)	(75)	
Month 6	155.5 ± 5.5	162.4 ± 4.4	149.9 ± 7.6	0.365
	[1.76 ± 0.06]	[1.83 ± 0.05]	[1.69 ± 0.09]	
	(146)	(121)	(66)	
Month 12	155.9 ± 4.0[d]	172.5 ± 6.1[d, e]	136.8 ± 5.4	< 0.001
	[1.76 ± 0.05]	[1.95 ± 0.07]	[1.55 ± 0.06]	
	(136)	(107)	(65)	

a: Mean value is the mean on-therapy value. SEM is the standard error of the mean.
b: Adjusted mean values ± SEM in mg/dL.
c: Number of patients.
d: Pairwise significant p-value comparison for a Rapamune treatment group versus azathioprine.
e: Pairwise significant p-value comparison for 2 mg/day Rapamune versus 5 mg/day Rapamune treatment group.
f: Pairwise significant p-value comparison for placebo versus azathioprine treatment group.

The incidence of increased creatinine level reported as an adverse event by investigators was not significantly different across treatment groups. For study 301, the rates were 35% for the Rapamune 2 mg/day group, 37% for the Rapamune 5 mg/day group, and 28% for the azathioprine

group. For study 302, the rates were 39% for the Rapamune 2 mg/day group, 40% for the Rapamune 5 mg/day group, and 38% for the placebo group. These rates are comparable to or lower than those reported for the tacrolimus renal trial[6] (45% and 42% in the tacrolimus and CsA groups, respectively).

The mechanism(s) leading to the higher creatinine values in Rapamune-treated groups are not completely defined. Patients who withdrew from therapy were not included in these analysis of mean creatinine levels over time. The on-therapy analysis may have led to a selection bias against Rapamune, as the main cause of withdrawal in the placebo and azathioprine cohorts was efficacy failure from acute rejection (patients more likely to have a reduced GFR long term). Further, the higher creatinine values in the Rapamune-treated patients may reflect enhanced CsA nephrotoxicity as Rapamune appears not to have intrinsic nephrotoxic effects.

8.7.2.4 Conclusions

- Rapamune lacks inherent nephrotoxicity, as shown in
    - * animal models
    - * phase II trials of Rapamune as primary therapy in de novo renal transplant patients
    - * phase II trials in which Rapamune was used as monotherapy for psoriasis.
- Patients treated with full-dose CsA and Rapamune had higher creatinine levels over time than patients treated with full-dose CsA plus placebo or azathioprine.
    - * Creatinine levels were slightly higher in the Rapamune 5 mg/day cohort than in the 2 mg/day group, indicating a dose relationship.
    - * On-therapy creatinine values in the Rapamune 2 mg/day group remained stable between months 3 and 12.
    - * Higher creatinine levels most likely represent enhanced CsA nephrotoxicity as Rapamune has no intrinsic nephrotoxicity.
    - * A selection bias against Rapamune (section 8.7.2.3) in the "on-therapy" analysis cannot be ruled out.

- As discussed (Section 8.7.2), constraints within the design of the phase 3 trials prevented the investigators from lowering the CsA dose in cases of suspected toxicity as standard clinical practice would have dictated.

8.7.3 Lipids

8.7.3.1 Background

Hyperlipidemia is common in the transplant population due to the high frequency of preexisting comorbid conditions and concurrent therapies. This section will review the effects of Rapamune, when coadministered with CsA and corticosteroids, on cholesterol and triglycerides and discuss potential clinical sequelae of hyperlipidemia.

8.7.3.2 TEAE for Hyperlipidemia

Hypercholesteremia and hyperlipemia (hypertriglyceridemia) are more commonly reported as TEAE in the Rapamune-treated groups. The following are results from the cumulative data base (≥ 12 months). For study 301, hypercholesteremia was reported for 38% of the patients in the Rapamune 2 mg/day group, for 42% of the patients in the Rapamune 5 mg/day group, and 33% in the azathioprine group. The differences were not statistically significant. For study 302, hypercholesteremia was reported for 43% of the patients in the Rapamune 2 mg/day group, 46% of the patients in the Rapamune 5 mg/day group, and 23% of the patients in the placebo group. The differences were significant for both Rapamune groups compared with the placebo group.

The following results are from the cumulative data base (≥ 12 months). For study 301, hypertriglyceridemia (hyperlipemia) was reported for 38% of the patients in the Rapamune 2 mg/day group, for 44% of the patients in the Rapamune 5 mg/day group, and for 28% of the patients in the azathioprine group. The differences were significant for both Rapamune groups compared with the azathioprine group. For study 302, hypertriglyceridemia occurred in 45% of the patients in the Rapamune 2 mg/day group, 57% of the patients in the Rapamune 5 mg/day group, and 23% of the patients in the placebo group. The rates were significantly higher for both Rapamune groups compared with the placebo group, and for the 5 mg/day group compared with the 2 mg/day group.

Despite the frequent reporting of TEAEs related to lipids, discontinuation for the reasons of hyperlipemia or hypercholesteremia was distinctly uncommon, affecting only 0.4% of patients in the 2 mg/day group and 2.5% of patients in the 5 mg/day group (combined 301 and 302 data).

TABLE 8.7.3.2A. NUMBER (%) OF PATIENTS WITH TREATMENT-EMERGENT ADVERSE EVENTS FOR HYPERLIPIDEMIA (STUDIES 301 AND 302)

	Treatment Groups			
Study/Event	Rapamune 2 mg/day	Rapamune 5 mg/day	Azathioprine	Placebo
301	n = 281	n = 269	n = 160	N/A
Hypercholesteremia	108 (38)	113 (42)	53 (33)	N/A
Hyperlipemia	106 (38)	118 (44)	45 (28)	N/A
302	n = 218	n = 208	N/A	n = 124
Hypercholesteremia	94 (43)	96 (46)	N/A	28 (23)
Hyperlipemia	98 (45)	118 (57)	N/A	28 (23)

Elevated serum lipid levels may have a role in the pathophysiology of myocardial infarction, cerebrovascular accident, and pancreatitis. These events occurred at similar rates in both Rapamune and control groups (Table 8.7.3.2B.).

TABLE 8.7.3.2B. INCIDENCE OF TREATMENT-EMERGENT ADVERSE EVENTS WITH A HISTORICAL RELATIONSHIP TO HYPERLIPIDEMIA (STUDIES 301 AND 302 COMBINED, ≥ 12 MONTHS)

Event	Rapamune 2 mg/day n = 499	Rapamune 5 mg/day n = 477	Azathioprine n = 160	Placebo n = 124
Pancreatitis	7 (1.4%)	2 (0.4%)	2 (1.3%)	1 (0.8%)
Myocardial infarction	8 (1.6%)	8 (1.7%)	2 (1.3%)	0
Cerebrovascular accident	7 (1.4%)	8 (1.7%)	4 (2.5%)	1 (0.8%)

8.7.3.3 Mean Lipid Values

As shown in Figures 8.7.3.3A and 8.7.3.3B, serial serum lipid values measured through 12 months reveal that the magnitude of the disparity in mean lipid values between the Rapamune and control groups tends to diminish, so much so that at month 12 the mean fasting cholesterol values were no longer significantly higher in the Rapamune 2 mg/day group than in the placebo group. Similarly, the month 12 mean fasting triglyceride values were no longer significantly higher in the Rapamune 2 mg/day group than in the azathioprine group. Multiple factors probably contribute to this phenomenon, including protocol-specified reductions in CsA and corticosteroid doses, reduction in Rapamune doses for some patients, and the use of nonpharmacologic (diet and exercise) and pharmacologic modalities to control high lipid levels.

The number of patients in each treatment group at each timepoint shown in these figures is presented in Tables 8.7.3.3A and 8.7.3.3B, respectively.

TABLE 8.7.3.3A. NUMBER OF PATIENTS IN EACH TREATMENT GROUP AT EACH TIMEPOINT IN FIGURE 8.7.3.3A.

		Months						
Treatment Groups	Baseline	1	2	3	4	6	9	12
Rapamune 2 mg/day	415	415	278	254	245	223	214	199
Rapamune 5 mg/day	401	401	253	248	235	206	204	179
Azathioprine	131	131	64	60	58	45	55	47
Placebo	107	107	63	63	54	53	56	51

FIGURE 8.7.3.3A. CRUDE MEAN CHOLESTEROL VALUES OVER TIME (ANCOVA P VALUES ARE FOR THE COMPARISON OF ADJUSTED MEANS)

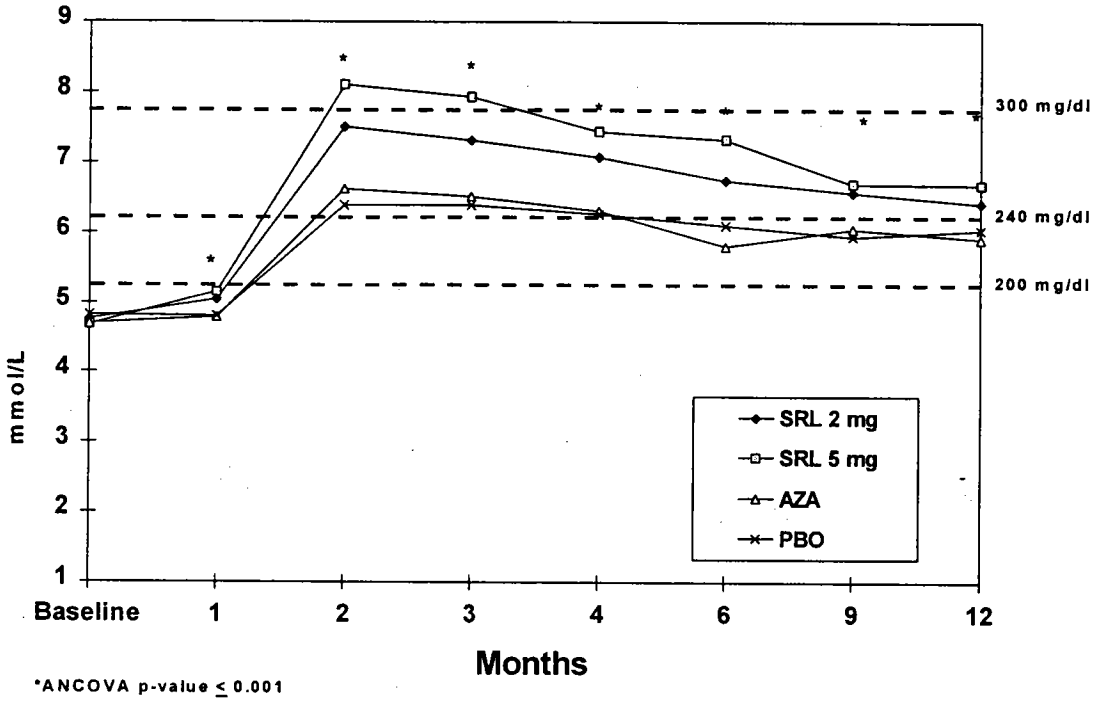
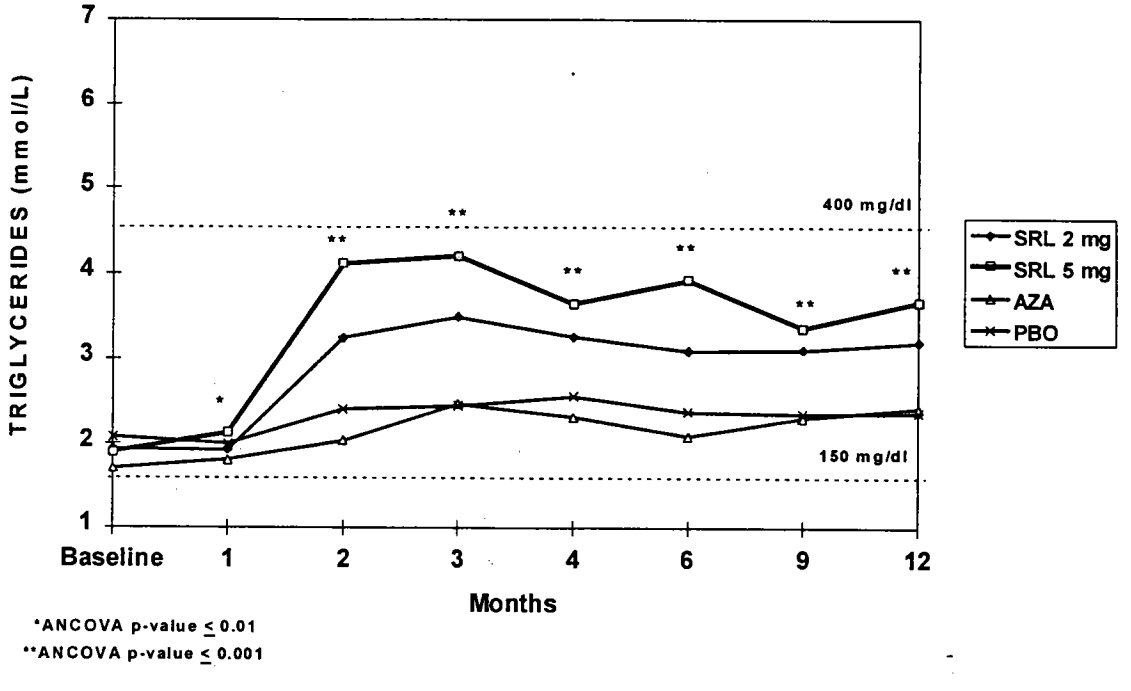


TABLE 8.7.3.3B. NUMBER OF PATIENTS IN EACH TREATMENT GROUP AT EACH TIMEPOINT IN FIGURE 8.7.3.3B

		Months						
Treatment Groups	Baseline	1	2	3	4	6	9	12
Rapamune 2 mg/day	414	414	266	238	235	221	209	198
Rapamune 5 mg/day	402	402	240	237	226	195	195	174
Azathioprine	129	129	56	54	52	44	50	43
Placebo	107	107	61	62	53	52	56	50

FIGURE 8.7.3.3B. CRUDE MEAN TRIGLYCERIDE VALUES OVER TIME (ANCOVA P VALUES ARE FOR THE COMPARISON OF ADJUSTED MEANS)



8.7.3.4 Adjusted Mean Lipid Values By Study

Adjusted mean fasting serum cholesterol and triglyceride values are presented separately for studies 301 and 302 below. Only the results from months 1, 3, 6, and 12 are presented.

8.7.3.4.1 Cholesterol

The results from the two studies are generally consistent, and are presented below in Tables 8.7.3.4.1A and B. It should be noted that at month 12, there is no longer any significant difference between treatment groups in study 301. In study 302 the mean fasting cholesterol remains

significantly higher in the Rapamune 5 mg/day group compared to the Rapamune 2 mg/day group and placebo.

TABLE 8.7.3.4.1A. ADJUSTED MEAN VALUES (± SEM) FOR SERUM FASTING CHOLESTEROL (mmol/L) STUDY 301

	Treatment Group			
Time	Rapamune 2 mg/day	Rapamune 5 mg/day	Azathioprine	ANCOVA
Month 1	4.89 ± 0.07[a]	5.10 ± 0.0[d]	4.73 ± 0.09	0.002
	[189 ± 2.7][b]	[197 ± 2.7]	[183 ± 3.5]	
	(219)[c]	(216)	(131)	
Month 3	7.08 ± 0.17[d]	8.03 ± 0.17[d]	6.42 ± 0.24	< 0.001
	[274 ± 6.6]	[311 ± 6.6]	[248 ± 9.3]	
	(114)	(120)	(60)	
Month 6	6.66 ± 0.16[d]	7.20 ± 0.16[d]	5.80 ± 0.24	< 0.001
	[258 ± 6.2]	[278 ± 6.2]	[224 ± 9.3]	
	(100)	(105)	(45)	
Month 12	6.39 ± 0.17	6.53 ± 0.17	5.86 ± 0.23	0.063
	[247 ± 6.6]	[253 ± 6.6]	[227 ± 8.9]	
	(84)	(87)	(47)	

a: Mean value is the mean on-therapy value. SEM is the standard error of the mean.

b: Adjusted mean values ± SEM in mg/dL.

c: Number of patients.

d: Pairwise significant p-value comparison for a Rapamune treatment group versus azathioprine.

TABLE 8.7.3.4.1B. ADJUSTED MEAN VALUES (± SEM) FOR FASTING CHOLESTEROL (mmol/L) STUDY 302

Time	Rapamune 2 mg/day	Rapamune 5 mg/day	Placebo	ANCOVA p-Value
Month 1	5.183 ± 0.058[a, d] [200 ± 2.2][b] (196)[c]	5.252 ± 0.059[d] [203 ± 2.3] (185)	4.838 ± 0.078 [187 ± 3.0] (107)	< 0.001
Month 3	7.492 ± 0.148[d] [290 ± 5.7] (140)	7.915 ± 0.155[d, e] [306 ± 6.0] (128)	6.387 ± 0.221 [247 ± 8.5] (63)	< 0.001
Month 6	6.811 ± 0.131[d] [263 ± 5.1] (123)	7.482 ± 0.145[d, e] [289 ± 5.6] (101)	6.111 ± 0.200 [236 ± 7.7] (53)	< 0.001
Month 12	6.426 ± 0.137 [248 ± 5.3] (115)	6.904 ± 0.153[d, e] [267 ± 5.9] (92)	6.046 ± 0.205 [234 ± 7.9] (51)	0.003

a: Mean value is the mean on-therapy value. SEM is the standard error of the mean.
b: Adjusted mean values ± SEM in mg/dL.
c: Number of patients.
d: Pairwise significant p-value comparison for a Rapamune treatment group versus placebo.
e: Pairwise significant p-value comparison for 2 mg/day Rapamune versus 5 mg/day Rapamune treatment group.

8.7.3.4.2 Triglycerides

The results from the two studies are generally consistent, and are presented below in Tables 8.7.3.4.2A and B. It should be noted that at month 12, there is no longer any significant difference between treatment groups in study 301. In study 302 the mean fasting triglycerides remains significantly higher in the Rapamune 5 mg/day group compared to the Rapamune 2 mg/day group and placebo.

TABLE 8.7.3.4.2A. ADJUSTED MEAN VALUES (± SEM) FOR SERUM FASTING TRIGLYCERIDES (mmol/L) STUDY 301

	Treatment Group			
Time	Rapamune 2 mg/day	Rapamune 5 mg/day	Azathioprine	ANCOVA
Month 1	1.65 ± 0.07[a] [146 ± 6.2][b] (218)[c]	1.97 ± 0.07[d] [175 ± 6.2] (217)	1.82 ± 0.09 [161 ± 8.0] (129)	0.004
Month 3	3.43 ± 0.32 [304 ± 28.3] (102)	4.49 ± 0.30[d, e] [398 ± 26.6] (112)	2.48 ± 0.43 [220 ± 38.1] (54)	< 0.001
Month 6	3.20 ± 0.30[e] [283 ± 26.6] (98)	4.12 ± 0.30[d, e] [365 ± 26.6] (96)	2.10 ± 0.44 [186 ± 39.0] (44)	< 0.001
Month 12	3.28 ± 0.28 [291 ± 24.8] (83)	3.52 ± 0.29 [312 ± 25.7] (81)	2.61 ± 0.39 [231 ± 34.5] (43)	0.174

a: Mean value is the mean on-therapy value. SEM is the standard error of the mean.
b: Adjusted mean values ± SEM in mg/dL.
c: Number of patients.
d: Pairwise significant p-value comparison for 2 mg/day Rapamune versus 5 mg/day Rapamune treatment group.
e: Pairwise significant p-value comparison for a Rapamune treatment group versus azathioprine.

TABLE 8.7.3.4.2B. ADJUSTED MEAN VALUES (± SEM) FOR FASTING TRIGLYCERIDES (mmol/L) STUDY 302

Time	Rapamune 2 mg/day	Rapamune 5 mg/day	Placebo	ANCOVA p-Value
Month 1	2.193 ± 0.058[a] [194 ± 5.1][b] (196)[c]	2.293 ± 0.060[d] [203 ± 5.3] (185)	2.016 ± 0.079 [179 ± 7.0] (107)	0.021
Month 3	3.488 ± 0.167[d] [309 ± 14.8] (136)	4.000 ± 0.174[d, e] [354 ± 15.4] (125)	2.388 ± 0.247 [212 ± 21.9] (62)	< 0.001
Month 6	3.035 ± 0.148[d] [269 ± 13.1] (123)	3.693 ± 0.165[d, e] [327 ± 14.6] (99)	2.345 ± 0.228 [208 ± 20.2] (52)	< 0.001
Month 12	3.054 ± 0.191 [271 ± 16.9] (115)	3.769 ± 0.212[d, e] [334 ± 18.8] (93)	2.386 ± 0.289 [211 ± 25.6] (50)	< 0.001

a: Mean value is the mean on-therapy value. SEM is the standard error of the mean.
b: Adjusted mean values ± SEM in mg/dL.
c: Number of patients.
d: Pairwise significant p-value comparison for a Rapamune treatment group versus placebo.
e: Pairwise significant p-value comparison for 2 mg/day Rapamune versus 5 mg/day Rapamune treatment group.

8.7.3.5 Risk Factors for On-Therapy Hyperlipidemia

To further characterize the risk factors and course of the lipid abnormalities experienced by patients in the trial, a number of additional analyses have been performed: multivariate logistic regression of demographic variables as predictors of treatment-emergent hyperlipidemia, frequency of hyperlipidemia, analysis of recovery, and response to lipid lowering therapies.

Multivariate logistic regression analysis examined the effect of age, gender, race, fasting glucose, baseline (before transplant) lipid values, and Rapamune dose on presentation with high cholesterol (> 6.19 mmol/L, ~ 240 mg/dL) or triglyceride (> 4.5 mmol/L, ~ 400 mg/dL). Of these variables, only high baseline values of triglyceride and cholesterol are associated with increased odds for high on-therapy measurements, as is the highest Rapamune dose. The summary statistics for logistic regression of lipid elevations for these risk factors are presented in Table 8.7.3.5A.

TABLE 8.7.3.5A. SUMMARY STATISTICS FOR LOGISTIC REGRESSION OF LIPID ELEVATIONS[a]

	Triglycerides		Cholesterol	
Variable	Odds Ratio	p-Value	Odds Ratio	p-value
Rapamune 2 mg/day[b]	3.15	< 0.001	2.76	< 0.001
Rapamune 5 mg/day[c]	5.19	< 0.001	3.50	< 0.001
Baseline value[d]	4.07	< 0.001	2.73	< 0.001
Pearson goodness of fit[e]		0.361		0.032

a: For the risk factors of high baseline triglyceride and cholesterol levels.
b: Rapamune 2 mg vs all comparators.
c: Rapamune 5 mg vs all comparators.
d: Baseline value for triglycerides was dichotomized as > 1.69, ≤ 1.69; elevation was defined as > 4.5.; baseline value for cholesterol was dichotomized as > 5.18 , ≤ 5.18; elevation was defined as > 6.19.
e: Pearson Goodness of Fit test; values < 0.05 indicate lack of fit of model.

8.7.3.6 Frequency of Hyperlipidemia

The phase 3 studies were not designed for the prospective diagnosis of hyperlipidemia. Nevertheless, there were likely more cases of hyperlipidemia in the Rapamune treatment groups, as evidenced by increased frequency of the discretionary use of lipid-lowering drugs among Rapamune-treated patients, the increased frequency of high triglyceride and cholesterol values at clinic visits over time, and the increased proportion of patients in the Rapamune groups with one or more measured lipid abnormalities. This is shown in Figures 8.7.3.6A and B. The number of patients in each treatment group at each timepoint shown in these figures is presented in Tables 8.7.3.6A and 8.7.3.6B, respectively.

TABLE 8.7.3.6A. NUMBER OF PATIENTS IN EACH TREATMENT GROUP AT EACH TIMEPOINT IN FIGURE 8.7.3.6A.

		Months			
Treatment Groups	Baseline	1	3	6	12
Rapamune 2 mg/day	415	415	254	223	199
Rapamune 5 mg/day	401	401	248	206	179
Azathioprine	131	131	60	45	47
Placebo	107	107	63	53	51

FIGURE 8.7.3.6A. PERCENT OF PATIENTS WITH CHOLESTEROL > 6.19 mmol/L (240 mg/dL) AT EACH CLINIC VISIT (STUDIES 301 AND 302 COMBINED)

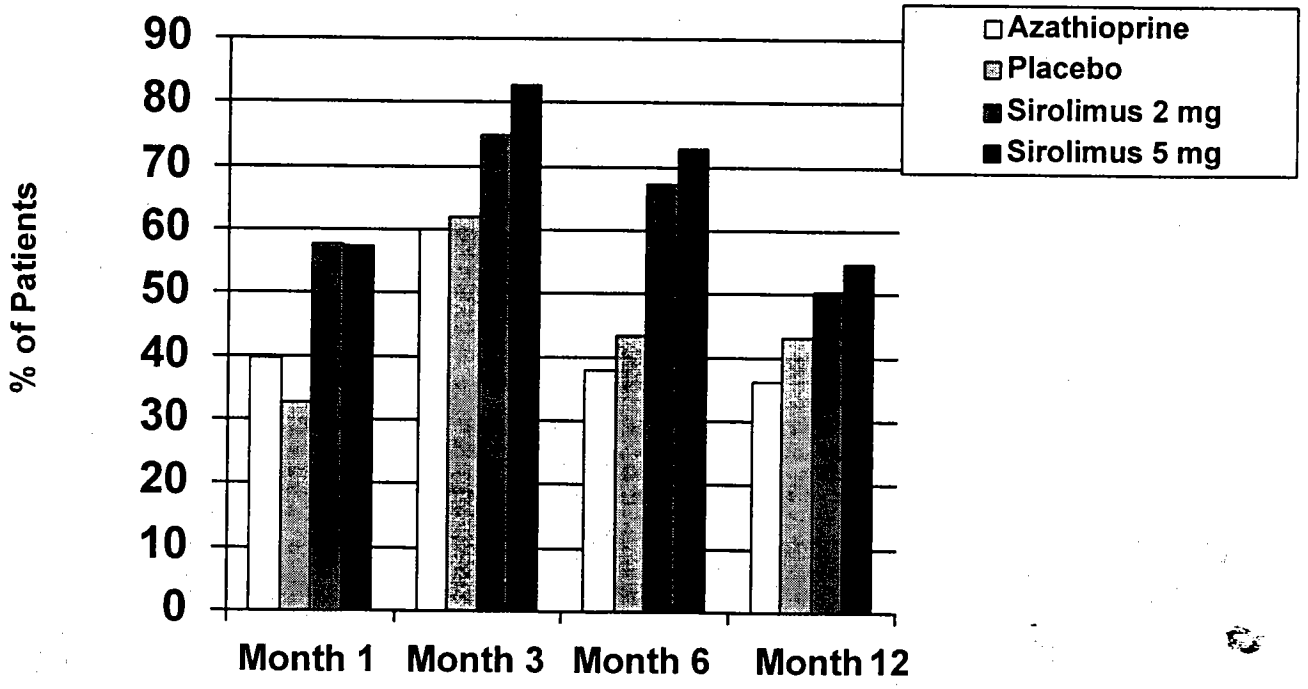
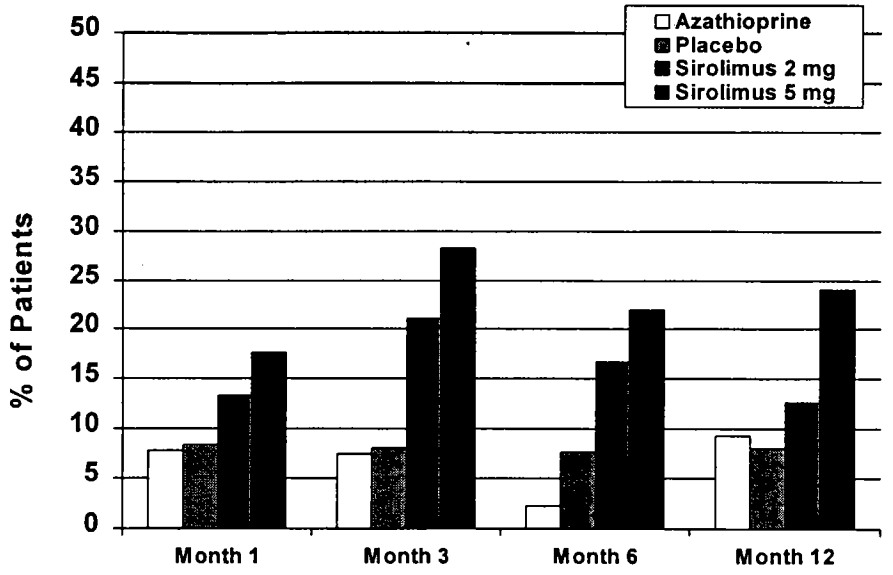


TABLE 8.7.3.6B. NUMBER OF PATIENTS IN EACH TREATMENT GROUP AT EACH TIMEPOINT IN FIGURE 8.7.3.6B.

		----------Months----------			
Treatment Groups	Baseline	1	3	6	12
Rapamune 2 mg/day	414	414	238	221	198
Rapamune 5 mg/day	402	402	237	195	174
Azathioprine	129	129	54	44	43
Placebo	107	107	62	52	50

FIGURE 8.7.3.6B. PERCENT OF PATIENTS WITH TRIGLYCERIDES > 4.5 mmol/L (400 mg/dL) AT EACH CLINIC VISIT (STUDIES 301 AND 302 COMBINED)



Mean cholesterol and triglyceride values were highest in the 5 mg/day Rapamune group, peaked at month 2, and decreased after month 3 (Figures 8.7.3.3A and B). Additional analysis of the subset of patients who contributed data at all clinic visits confirms this trend.

8.7.3.7 Recovery Analysis

For the subset of patients who had a high triglyceride or cholesterol value and a second follow-up measurement during the first 6 months of therapy, "recovery" to triglyceride values below 4.5 mmol/L (~ 400 mg/dL) and cholesterol values below 6.19 mmol/L (~ 240 mg/dL) was examined. The results for triglycerides and cholesterol are shown in Figures 8.7.3.7A and B, respectively. Most patients with high values recovered; ie, on follow-up, approximately 80% of those with elevated

triglyceride levels and approximately 60% of those with elevated cholesterol levels had values below 4.5 mmol/L and 6.19 mmol/L, respectively. Moreover, the percentage of patients improving was the same in each treatment group; similar rates of improvement were seen in the subset of patients who received no lipid lowering drug.

FIGURE 8.7.3.7A. RECOVERY FROM HIGH TRIGLYCERIDE LEVELS MEASURED DURING THE FIRST 6 MONTHS (STUDIES 301 AND 302 COMBINED)

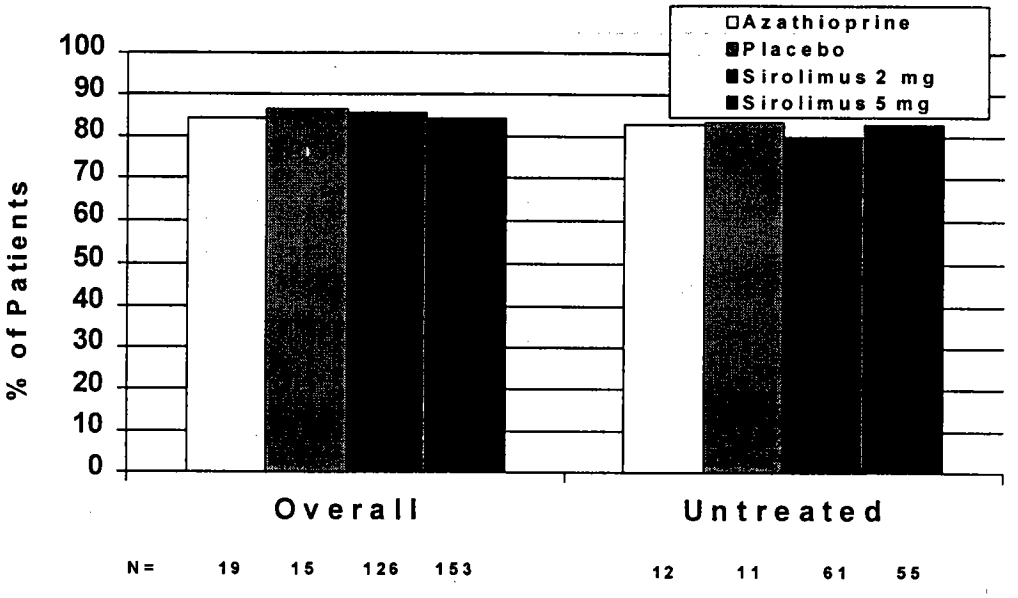
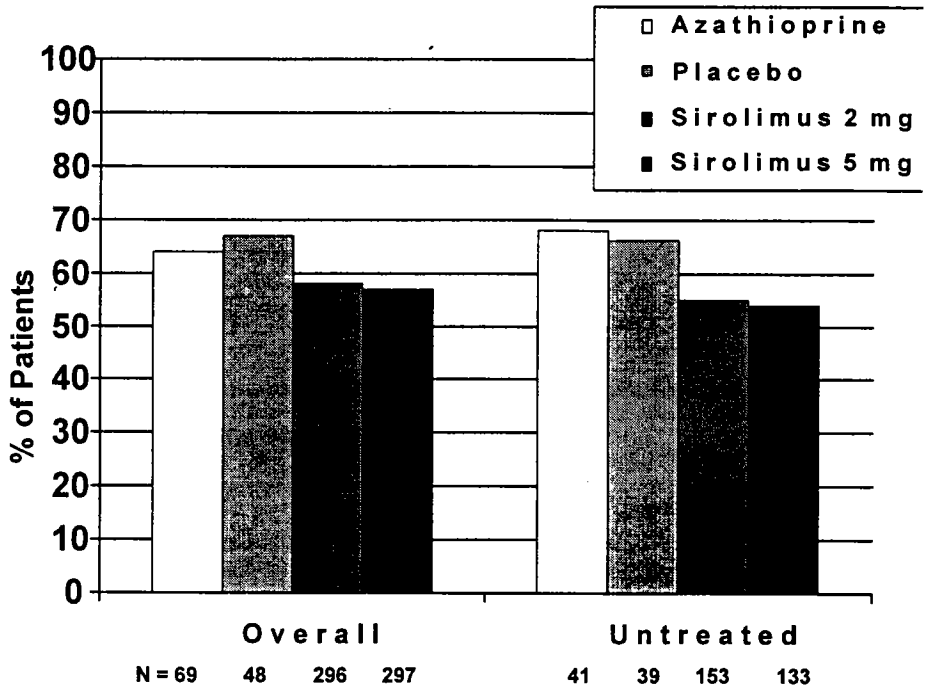


FIGURE 8.7.3.7B. RECOVERY FROM HIGH CHOLESTEROL LEVELS MEASURED DURING THE FIRST 6 MONTHS (STUDIES 301 AND 302 COMBINED)



8.7.3.8 Countermeasure Therapy

Lipid lowering drugs were prescribed ad libitum for the treatment of hyperlipidemia, using local practice criteria. Table 8.7.3.8A illustrates that the use of lipid lowering agents was more frequent in the Rapamune treatment groups.

TABLE 8.7.3.8A. CUMULATIVE USE OF LIPID LOWERING AGENTS: (STUDIES 301 AND 302 COMBINED)

	Rapamune 2 mg/day		Rapamune 5 mg/day		Azathioprine	Placebo
Lipid Lowering Agents	301 (n = 284)	302 (n = 227)	301 (n = 274)	302 (n = 219)	301 (n = 161)	302 (n = 130)
HMG-CoA reductase inhibitors	137 (48.2)	97 (42.7)	146 (53.2)	94 (42.9)	50 (31.0)	22 (16.9)
Fibrates	34 (11.9)	20 (8.8)	36 (13.1)	23 (10.5)	8 (4.9)	4 (3.0)

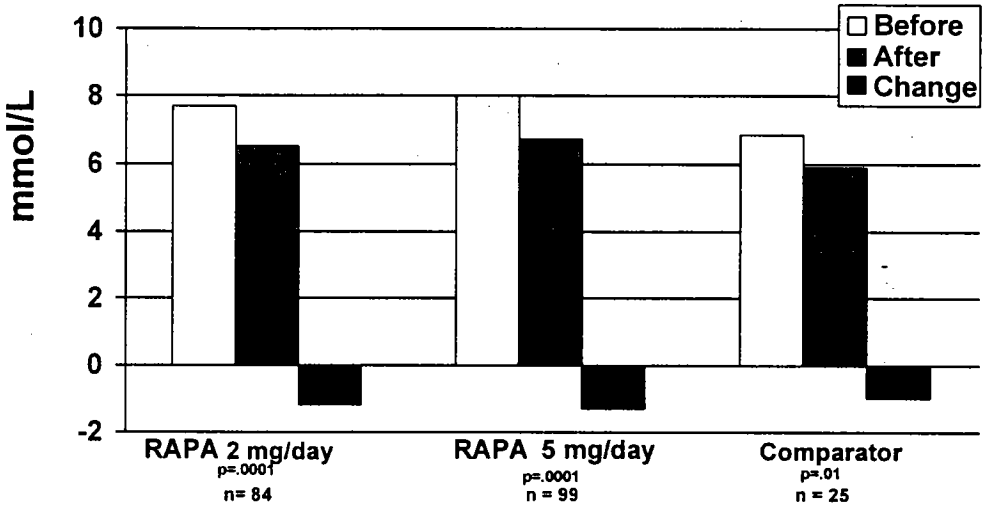
8.7.3.8.1 Cholesterol

The response of cholesterol levels to lipid lowering medications during the first 6 months of the study was also examined. HMG-CoA reductase inhibitors were the pharmacotherapeutic agents received by the majority of patients who were treated for hyperlipidemia. Lipid-lowering agents were

well tolerated, with a single instance of rhabdomyolysis reported for a patient randomly assigned to receive azathioprine (without Rapamune); TEAE reports for elevated CPK were comparable among treatment groups.

A subset of patients was identified who had lipid lowering agents introduced during the study, had serum cholesterol and/or triglyceride values measured at that time, and had repeat serum cholesterol and/or triglyceride values measured 8 or more weeks later. This subset of patients, treated with an HMG-CoA reductase inhibitor, had a significant reduction of mean cholesterol value on repeat measurement, as shown in Figure 8.7.3.8.1A. The magnitude of this response was similar across all groups. No significant response of triglyceride to HMG-CoA reductase inhibitors could be demonstrated in this analysis (data not shown).

FIGURE 8.7.3.8.1A. CHOLESTEROL RESPONSE TO HMG CoA REDUCTASE INHIBITORS (STUDIES 301 AND 302 COMBINED; COMPARATOR IS AZATHIOPRINE AND PLACEBO COMBINED)



8.7.3.8.2 Triglycerides

Treatment response 8 weeks after the introduction of fibrates was evaluable for 6 patients on placebo or azathioprine, 25 patients randomized to 2 mg/day Rapamune, and 30 patients randomized to 5 mg/day Rapamune. Of the 6 patients on comparator (azathioprine or placebo) treated with fibrates, 2 patients responded with a decrease in triglyceride of ≥ 1 mmol/L; 10 of 25 patients in the 2 mg/day Rapamune arm treated with fibrates and 19 of 30 patients randomized to 5 mg/day of Rapamune had treatment responses of this magnitude. Few patients were treated with fibrates; therefore, the number of data points available to explore the statistical significance of the intervention was small. However, it appears that both cholesterol and triglyceride values decreased in response to fibrates.

8.7.3.9 Summary

- A significantly greater proportion of the patients in the Rapamune treatment groups had elevated serum cholesterol and triglyceride values than in the comparator groups. Lipid abnormalities were more frequent and the values were higher in the Rapamune 5 mg/day group than in the Rapamune 2 mg/day group.

- During the first year after transplant, a high proportion of patients recover from hyperlipidemia, regardless of treatment group. Patients in the Rapamune cohorts were more likely to have received lipid-lowering therapies than those in other groups.

- Logistic regression analysis of demographic factors indicates that high on-therapy cholesterol and triglyceride values are more likely to occur in patients with elevated baseline cholesterol and triglyceride values.

- Elevated lipids were not associated with increases in the reported incidence of major vascular events or pancreatitis. Few patients were withdrawn from treatment with Rapamune because of elevations of serum triglyceride or cholesterol.

- Response of elevated cholesterol levels to HMG-CoA reductase inhibitor therapy was similar among the treatment groups. The triglyceride levels in the small number of patients treated with fibrates also decreased.

- The concomitant administration of Rapamune with lipid lowering agents (fibrates or HMG-CoA reductase inhibitors) was well tolerated. No cases of rhabdomyolysis were reported in the Rapamune groups.

8.7.4 Hematology

8.7.4.1 Background

Hematologic toxicity is one of the major adverse events associated with many approved immunosuppressive agents.[43] The myelosuppressive properties of MMF and azathioprine have been well described. The antilymphocyte antibodies are known to induce thrombocytopenia. Hemolytic-uremic syndrome (HUS) has been seen after administration of CsA, tacrolimus, and OKT3.[44,45,46]

In this section, the effects of Rapamune treatment on platelets, white cell counts, and hemoglobin are reviewed. Particular emphasis is placed on the percentage of patients who had dose reductions or discontinued study drug because of hematologic abnormalities. The occurrence of HUS in the phase 3 trials and the attendant clinical consequences are also discussed. Patients diagnosed with either hemolytic uremic syndrome (HUS) or thrombotic thrombocytopenic purpura (TTP) were included under the designated COSTART diagnosis of TTP. Patients with either diagnosis are combined here in the overall category, HUS/TTP.

8.7.4.1.1 Anemia, Thrombocytopenia, and Leukopenia as TEAEs

Table 8.7.4.1A shows the incidence of anemia, leukopenia, and thrombocytopenia as TEAEs. Thrombocytopenia and anemia were more frequently reported in the Rapamune 5 mg/day group. Leukopenia was more commonly reported as an adverse event in patients who received azathioprine.

TABLE 8.7.4.1A. RATES (%) OF ANEMIA, LEUKOPENIA, AND THROMBOCYTOPENIA REPORTED AS ADVERSE EVENTS (STUDIES 301 AND 302, ≥ 12 MONTHS)

TEAE	Rapamune 2 mg/day (n = 499)	Rapamune 5 mg/day (n = 477)	Azathioprine (n = 160)	Placebo (n = 124)
Anemia	25	35[a]	29	21
Leukopenia	9	14[b]	20[c]	8
Thrombocytopenia	13	24[d]	9	9

a: $p < 0.05$, Rapamune 5 mg/day vs Rapamune 2 mg/day and azathioprine.
b: $p < 0.05$, Rapamune 5 mg/day vs Rapamune 2 mg/day.
c: $p < 0.05$, azathioprine vs Rapamune 2 mg/day and placebo.
d: $p < 0.05$, Rapamune 5 mg/day vs Rapamune 2 mg/day, azathioprine, and placebo.

However, discontinuation of study drug because of these adverse events was unusual (Table 8.7.4.1B). Rates of discontinuation were similar across treatment groups except for the significantly higher rate of withdrawal in the azathioprine group because of leukopenia.

TABLE 8.7.4.1B. DISCONTINUATION FROM STUDY MEDICATION (PERCENTAGE): STUDIES 301 AND 302, ≥ 12 MONTHS

Adverse Event	Rapamune 2 mg/day (n = 499)	Rapamune 5 mg/day (n = 477)	Azathioprine (n = 160)	Placebo (n = 124)
Anemia	0	0.6	0	0
Leukopenia	0.2	0.8	4.4[a]	0
Thrombocytopenia	0.6	1.7	1.9	0.8

a: $p < 0.05$, azathioprine vs Rapamune 2 and 5 mg/day and placebo.

The tabulation of discontinuations, presented here and in the 90-day safety update,[47] excludes patients if the diagnosis was noted at the screening visit as a pre-existing condition. Hence, patient 30210-1006, who discontinued therapy (Rapamune 5 mg/day) after 9 days because of leukopenia and thrombocytopenia, is not included in the tabulation because leukopenia and thrombocytopenia were noted on screening. However, the tabulation for dose reduction for anemia, thrombocytopenia, and leukopenia does not exclude patients with the diagnosis noted at screening.

8.7.4.2 Effect on Platelet Count

8.7.4.2.1 Results From Rapamune Phase 3 Trials

The major hematologic effect of Rapamune administration appears to be the occurrence of dose-related, reversible decreases in platelet count. The clinical consequences are mild and severe toxicity is rare.

Table 8.7.4.2.1A reviews the adjusted on-therapy mean platelet counts observed at months 1, 3, 6, and 12 in the phase 3 trials. The mean platelet counts are lower in the Rapamune treated patients, but well within the normal range (219 and 212 x 10^9/L in the Rapamune 2- and 5 mg/day groups at 12 months respectively).

TABLE 8.7.4.2.1A. ADJUSTED MEAN VALUES (± SEM) FOR PLATELET COUNT (10^9/L)

Time	Rapamune 2 mg/day	Rapamune 5 mg/day	Azathioprine	Placebo	ANCOVA p-Value
Month 1	198.0 ± 1.7[a,c,e] (496)[b]	189.6 ± 1.8[c,d] (471)	207.9 ± 3.1 (157)	200.6 ± 3.5 (124)	< 0.001
Month 3	229.8 ± 3.2[c,e] (377)	212.1 ± 3.3[c,d] (347)	249.8 ± 6.5 (88)	244.4 ± 7.1 (75)	< 0.001
Month 6	230.6 ± 3.4[e] (321)	216.1 ± 3.7[c,d] (282)	239.0 ± 6.9 (79)	243.6 ± 7.6 (66)	< 0.001
Month 12	218.5 ± 3.6[c] (273)	212.4 ± 3.8[c,d] (241)	235.5 ± 6.7 (77)	229.1 ± 7.4 (64)	0.012

a: Adjusted mean value is the mean on-therapy value for a patient with an average baseline. SEM is the standard error of the adjusted mean.
b: Number of pairs used for adjusted mean.
c: Pairwise significant p-value comparison for a Rapamune treatment group versus azathioprine.
d: Pairwise significant p-value comparison for a Rapamune treatment group versus placebo.
e: Pairwise significant p-value comparison for 2 mg/day Rapamune versus 5 mg/day Rapamune treatment group.

Severe thrombocytopenia was rare with no patients with platelet counts under 50 x 10^9/L after month 3. After month 3, greater than 98% of the patients in all groups had platelet counts above 100 x 10^9/L.

Only 2 patients recorded an on-therapy platelet count less than 20 x 10^9/L at any time during the first year of follow up.

Neither of these patients was reported to have any bleeding episodes.

Dose reduction for thrombocytopenia was more frequent in the Rapamune groups, but rarely led to study drug discontinuation, as shown in Table 8.7.4.2.1B. Further, the majority of patients in the Rapamune arms who discontinued study drug because of thrombocytopenia actually were diagnosed with HUS/TTP. Two (2) of 3 patients in the Rapamune 2 mg/day group and 6 of 8 patients in the Rapamune 5 mg/day group were diagnosed with HUS/TTP. The percentage of patients in each group who discontinued because of thrombocytopenia but without a diagnosis of HUS/TTP (1 and 2 patients in the Rapamune 2 and 5 mg/day groups, respectively) is shown in the third row of the table. Three (3) patients in the azathioprine cohort discontinued therapy because of thrombocytopenia; all 3 were also reported to have concurrently discontinued medication because of leukopenia.

TABLE 8.7.4.2.1B. RATE OF DOSE REDUCTION AND DISCONTINUATION FROM STUDY MEDICATION (PERCENT) AS A RESULT OF THROMBOCYTOPENIA: STUDIES 301 AND 302 COMBINED, ≥ 12 MONTHS

Dose Reduction and Discontinuation	Rapamune 2 mg/day (n = 499)	Rapamune 5 mg/day (n = 477)	Azathioprine (n = 160)	Placebo (n = 124)
Dose reduction and discontinuation[a]	4.0%	13.2%	1.9%	2.4%
Permanent discontinuation[b]	0.6%	1.7%	1.9%	0.8%
Discontinuation without diagnosis of HUS/TTP[c]	0.2%	0.4%	1.9%	0.8%

a: Includes patients who had dose reductions and those who were temporarily or permanently discontinued from study medication.
b: Patients who were discontinued permanently from study medication.
c: Patients who were discontinued permanently from study medication and did not have a diagnosis of HUS/TTP.

Rapamune dose reduction or discontinuation generally results in improvement of the platelet counts, as discussed below (section 8.7.4.2.2).

8.7.4.2.2 Rapamune Dose Reduction and Platelet Counts

As noted in Table 8.7.4.2.1B, discontinuation (especially without concomitant HUS/TTP) due to thrombocytopenia was uncommon. Investigators were able to manage cases of thrombocytopenia conservatively or with dose reduction. Table 8.7.4.2.2A summarizes the platelet count records for the 3 patients in the Rapamune treatment groups who discontinued therapy because of thrombocytopenia. As shown, the platelet counts recovered after discontinuation of study drug.

TABLE 8.7.4.2.2A. PLATELET COUNT RECORDS FOR PATIENTS WHO DISCONTINUED STUDY DRUG BECAUSE OF THROMBOCYTOPENIA

8.7.4.2.3 Conclusions

- In the renal transplant population, there are many causes of thrombocytopenia (eg, the use of antilymphocytic antibodies or the presence of thrombotic thrombocytopenic purpura, etc).

    * In a patient with persistent or severe thrombocytopenia, especially with microangiopathic anemia and increase in creatinine, the diagnosis of HUS/TTP may need to be considered.

- Dose-related decreases in platelet count were seen in the Rapamune treatment groups.

- Dose reduction because of thrombocytopenia was most prevalent in the Rapamune 5 mg/day group (13.2%), but rarely led to discontinuation (1.7%).
- Thrombocytopenia was generally reversible after dose reduction or discontinuation.
- Severe thrombocytopenia (< 20 x 10^9/L) was rare (0.2%, both Rapamune treatment groups).

8.7.4.3 Effects on White Blood Cells and Hemoglobin

8.7.4.3.1 Results from Rapamune Phase 3 Trials

There is a mild, dose-related effect of Rapamune on white cell counts; however, this effect is less pronounced than that of azathioprine. There were no cases of absolute neutropenia and no patients had a white cell count less than 1 x 10^9/L (1000/mm^3) recorded on therapy (90-day safety update data base) during the first year of study.

Dose reduction and the discontinuation of study medication because of leukopenia were highest in the azathioprine group (Table 8.7.4.3.1A).

TABLE 8.7.4.3.1A. RATE OF DOSE REDUCTION AND STUDY DRUG DISCONTINUATION (PERCENT) AS A RESULT OF LEUKOPENIA (STUDIES 301 AND 302 COMBINED, ≥ 12 MONTHS)

Dose Reduction and Discontinuation	Rapamune 2 mg/day (n = 499)	Rapamune 5 mg/day (n = 477)	Azathioprine (n = 160)	Placebo (n = 124)
Dose reduction[a]	3.4%	6.1%	10.6%	1.6%
Discontinuation[b]	0.2%	0.8%	4.4%	0

a: Includes patients who had dose reduction and temporary or permanent discontinuation of study medication

b: Patients who were discontinued permanently from study medication.

The mean on-therapy hemoglobin values were lower in the Rapamune 5 mg/day group; however, by month 12, the mean value in all groups was greater than 130 g/L.

The use of erythropoietin (1 month or more after transplantation) was captured in study 301; 14.2%, 8.4%, and 8.7% of the patients in the Rapamune 5 mg/day, 2 mg/day, and azathioprine groups, respectively, were treated with erythropoietin. This suggests that investigators were able to manage most cases of anemia with standard countermeasure therapy, since dose reduction and discontinuation of study medication because of anemia were rare in all treatment groups (Table 8.7.4.3.1B, data from studies 301 and 302 combined).

TABLE 8.7.4.3.1B. RATE OF DOSE REDUCTION AND STUDY DRUG DISCONTINUATION (PERCENT) AS A RESULT OF ANEMIA (STUDIES 301 AND 302 COMBINED, ≥ 12 MONTHS)

Dose Reduction and Discontinuation	Rapamune 2 mg/day (n = 499)	Rapamune 5 mg/day (n = 477)	Azathioprine (n = 160)	Placebo (n = 124)
Dose reduction[a]	0.4%	2.5%	1.9%	0
Discontinuation[b]	0	0.6%	0	0

a: Includes patients who had dose reduction and temporary or permanent discontinuation of study medication

b: Patients who were discontinued permanently from study medication.

8.7.4.3.2 Conclusions

8.7.4.3.2.1 White Blood Cells

- No patients in any treatment group demonstrated absolute neutropenia while on-therapy. This includes patients who have received treatment for one year or more.
- The effect of Rapamune on WBC was much less pronounced than that of azathioprine as evidenced by:
  - * The lowest mean white blood cell count was in the azathioprine group.
  - * A higher rate of discontinuation secondary to leukopenia was seen in the azathioprine group (4.4%) than in the Rapamune groups (less than 1%).

8.7.4.3.2.2 Hemoglobin

- Mean hemoglobin values were lower in the Rapamune 5 mg/day group but > 13 g/dL in all groups at 12 months.
- Dose reduction or patient discontinuation because of anemia were uncommon in all groups.

8.7.4.4 HUS/TTP

8.7.4.4.1 Rate of HUS/TTP in Phase 3 Trials

Table 8.7.4.4.1A shows the rate of HUS/TTP from studies 301 and 302 combined (cumulative data base). The percentage of patients for whom HUS/TTP resulted in graft loss or discontinuation of study medication is also shown. HUS/TTP was more frequent in the Rapamune 5 mg/day group than

in the 2 mg/day group. The rate in the Rapamune 2 mg/day group is comparable to the rate in the placebo and azathioprine groups. There were no patient deaths directly attributed to HUS/TTP and only 3 patients (2 in the Rapamune 5 mg/day group and 1 in the 2 mg/day group) lost their grafts secondary to HUS/TTP.

TABLE 8.7.4.4.1A. RATE (%) OF HUS/TTP IN STUDIES 301 AND 302 COMBINED, ≥ 12 MONTHS

	Rapamune			
Variable	2 mg/d (n = 499)	5 mg/d (n = 477)	Placebo (n = 124)	Azathioprine (n = 160)
HUS/TTP	2.0	5.4[a]	3.2	1.9
Discontinuation of study medication	1.0	4.4[b]	1.6	0
Graft loss	0.2	0.4	0	0
Patient deaths	0	0	0	0

a: $p < 0.05$, Rapamune 5 mg/day vs Rapamune 2 mg/day
b: $p < 0.05$, Rapamune 5 mg/day vs Rapamune 2 mg/day and azathioprine

As shown in Table 8.7.4.4.1B, the increased rate of HUS/TTP occurred primarily in study 302, where clustering of cases was seen among centers. Greater than 50% (14/27) of the cases were diagnosed at 3 centers. One center, center 30221, accounted for 22% of the cases. At this center, 6 of 18 randomized patients were diagnosed with HUS/TTP.

TABLE 8.7.4.4.1B. RATE (%) OF HUS/TTP STUDIES 301 AND 302, ≥ 12 MONTHS

Study	Rapamune 2 mg/day	Rapamune 5 mg/day	Placebo	Azathioprine
301[a]	1.4	2.6	N/A[c]	1.9
302	2.7	8.2[b]	3.2	N/A[c]

a: $p > 0.05$ across treatment groups
b: $p < 0.05$, Rapamune 5 mg/day vs 2 mg/day
c: Placebo was not used in study 301; azathioprine was not used in study 302.

In the 3 studies of Rapamune monotherapy mentioned above (section 8.7.2.2), no cases of HUS/TTP have been reported to date.

In CsA-treated patients rates of HUS/TTP ranging from 3% to 10% have been reported.[48]

8.7.4.4.2 Conclusions

- A higher rate of HUS/TTP was seen in patients receiving Rapamune 5 mg/day with full-dose CsA. The rate in the Rapamune 2 mg/day cohort was comparable to that in the control groups.

- This observed effect likely represents an exacerbation of a known CsA toxicity because:

  * HUS/TTP is a well described adverse event related to CsA therapy.

  * There have been no reports to date of HUS/TTP in studies where Rapamune monotherapy has been used.

- The rate of HUS/TTP was higher in study 302, where cases were seen to cluster among study centers.

- HUS/TTP was generally reversible with discontinuation of CsA, Rapamune, or both, and the use of standard therapy for HUS/TTP (plasma exchange, etc).

- No patient death was attributed to HUS/TTP and graft loss was rare.

8.8 Pharmacodynamic Safety Analysis Discussion

After adjusting for pertinent explanatory variables, positive significant associations were found between Rapamune exposure (measured by concurrent Rapamune trough concentrations) and the laboratory parameters hemoglobin, LDH, cholesterol, triglycerides, CPK, SGOT (AST), and serum creatinine. Platelet counts, serum potassium and Nankivell GFR had a negative association with Rapamune exposure. The effect of CsA exposure was not significant on CPK, SGOT (AST), serum potassium, and serum creatinine but otherwise it paralleled the Rapamune effect in all laboratory parameters, as discussed above, except for BUN for which Rapamune had no significant effect and CsA had a positive effect.

While the stepwise regression analysis indicated that several laboratory parameters might be influenced by high Rapamune trough concentrations and thus become a safety concern, the median-effect analysis seems to suggest that only the cholesterol level might be significantly elevated (above 6.19 mmol/L, [240 mg/dL]) within the therapeutic Rapamune concentration range, and the elevation may be substantial when the Rapamune concentration reached is above 30 ng/mL.

8.9 Vital Signs and Weight Data

No clinically important differences were seen among the treatment groups in vital signs measurements except weight. Mean weight was lower at months 3, 6, and 12 in the Rapamune 5 mg/day group than in the other groups.

8.10 Bone Density Assessments

There were no statistically significant differences in femoral neck or lumbar spine bone density measurements between therapy groups for males or females at 6 and 12 months.

8.11 Drug-Demographic Interactions

The TEAE profile and the frequency of potentially clinically important laboratory results were examined for patients in studies 301 and 302, stratified post hoc by age, sex, and ethnic origin. No differences of clinical concern were observed among age groups or between the sexes. However, clinically important differences were seen between black non-black patients and these are discussed (section 8.11.1). In addition, the safety and tolerance of oral Rapamune solution are described (section 8.11.2) in pediatric patients with chronic renal failure who were receiving hemodialysis or peritoneal dialysis.

8.11.1 Rapamune Therapy in Black Patients

Clinical trial and registry data show that black patients are at increased risk for acute rejection, a phenomenon associated with a complex set of biologic and epidemiologic features. These include decreased bioavailability of CsA,[49] diminished lymphocyte response to glucocorticoids,[50] greater prevalence of cadaveric donors, increased prevalence of high degree HLA mismatch, increased rate of delayed graft function (DGF), and younger average age at time of transplant[51]. Shortened allograft survival is also seen in this population.[52] Thus, while multidrug anti-rejection regimens are the rule for black patients, they continue to experience allograft rejection and chronic graft loss at higher rates than Caucasians and black patients appear less immunosuppressed relative to other patient populations.[53]

The goal of immunosuppressive therapy is to prevent acute rejection, an effect that may be achieved by increasing the intensity of immunosuppression, but must be balanced against the side-effects of immunosuppressant drugs. Results of the phase 2 dose-ranging study (study 203) demonstrated that compared to non-black patients, black patients are indeed at increased risk for

acute rejection when less intense immunosuppressant regimens were tested. Further, an imbalance in randomization of black patients led to difficulties interpreting the efficacy results of that study, and led to the decision to stratify randomization in the US phase 3 trial (study 301) by race. The randomization strategy was successful, with approximately equal numbers of black patients enrolled in each arm. About 10% of the patients enrolled in the global phase 3 trial (study 302) were black, and provide further supportive data regarding the effect of Rapamune in black patients.

The two pivotal trials tested the effect of 2 doses of Rapamune on a composite endpoint of acute rejection, graft loss or death at 6 months. In study 301 higher daily doses of CsA were administered to black patients to achieve troughs comparable to those in non-black patients. Corticosteroid doses were comparable in the two groups. Exposure to Rapamune was comparable for black and non-black patients for each dose tested. Nevertheless, higher rates of efficacy failure and acute rejection occurred in black patients on 2 mg/day Rapamune than in non-black patients. A positive treatment effect was consistent for black and non-black patients randomized to Rapamune 5 mg/day. The global phase 3 trial (study 302) included 66 black patients, who experienced a reduced rate of efficacy failure and acute rejection on Rapamune at either dose, and had results comparable to non-black trial participants. Treatment failure for black patients in study 302 was lowest in the 5 mg/day arm. Combined data from both trials show a rate of primary efficacy endpoint in black and non-black patients to be similar at 5 mg/day Rapamune.

Acute rejection may be an indicator of relative underimmunosuppression. The development of opportunistic infection or malignancy, in particular PTLD/lymphoma, may be a consequence of overimmunosuppression. In the phase 3 trials, a lower proportion of black patients developed PTLD/lymphoma during the trial and through month 36, with a single case occurring in a black patient in the azathioprine cohort. Similarly, few opportunistic infections were reported in black patients receiving Rapamune. Mycobacterial infection has been reported in two black patients in the Rapamune cohort. One case of pulmonary tuberculosis occurred 50 days after discontinuation of Rapamune while the patient was receiving MMF. One other case of a nontuberculous mycobacterial infection (*Mycobacterium haemophilum*) was reported in a black patient who received Rapamune; this patient had discontinued the trial after day 2 and was diagnosed with the infection nearly one year later while on tacrolimus. Premature discontinuation of prophylaxis for *Pneumocystis carinii* was associated with pneumonia in an elderly black male, who ultimately recovered; *Aspergillus* was also recovered from a bronchial lavage. Overall, herpesvirus and CMV occurred less frequently at either dose of Rapamune than in the MMF Tricontinental Trial. Black patients on either dose of Rapamune

had lower rates of *H. simplex, H. zoster*, pneumonia, sepsis, and all reported infections relative to "other" patients, primarily Caucasian. Despite the fact that black and non-black patients achieved similar trough concentrations of Rapamune, overall, it appears that Rapamune 5 mg/day does not pose a risk of over-immunosuppression to black patients.

Review of treatment-emergent adverse events for laboratory abnormalities showed that hypertriglyceridemia (hyperlipemia) was less frequently reported for black patients on 5 mg/day Rapamune than for "other" patients. Thrombocytopenia was reported less frequently for black patients on 5 mg/day than for "other" patients. Arthralgia was also less frequently reported for black patients in the 5 mg/day group than for "other" patients on either dose. Reports of leukopenia, anemia, and hypercholesteremia were similar for black patients and "other" patients. Overall, it appears that black patients may tolerate Rapamune, and in particular, the 5 mg/day dose of Rapamune, better than non-black patients.

Mean laboratory values in black patients at 6 months showed no significant change from baseline for white blood cell counts in patients receiving either 2 mg/day or 5 mg/day of Rapamune. A significant decrease in mean platelet count was seen in patients in the Rapamune 5 mg/day group, who had an acceptable mean platelet count of 205 x 10^9/L compared with the baseline platelet count of approximately 225 x 10^9/L. Mean fasting glucose levels and Nankivell GFR were comparable for black patients in both Rapamune groups. Cholesterol and triglyceride values in black patients were higher in the 5 mg/day group than the 2 mg/day group. However, the baseline triglyceride value in black patients in the 5 mg/day group was above normal, and therefore, this cohort was at greater risk for increased elevation of triglyceride on therapy (see section 8.7.3.5).

In summary, the 5 mg/day dose of Rapamune, administered with CsA and corticosteroid, allows black patients rejection-free survival at rates comparable to those for non-black patients, without the penalties associated with over-immunosuppression. Despite comparable exposure of black and non-black patients to Rapamune, there appears to be decreased risk of infection and lymphoma among black patients, possibly related to insensitivity to the effects of corticosteroids and decreased exposure to CsA. Laboratory abnormalities for black patients were of the same or lesser magnitude as those reported for non-black patients, and did not necessitate discontinuation of study drug administration. Thus, the 5 mg/day dose of Rapamune, in combination with CsA and corticosteroid, provides a beneficial treatment option for the black transplant population.

8.11.2 Pediatric Patients with Stable Chronic Renal Failure

One pediatric trial was conducted: Study 147 was a randomized, double-blind, placebo-controlled study of four ascending single oral doses of Rapamune solution. The objective was to determine the safety and tolerance of oral Rapamune solution in pediatric patients with renal failure who were receiving hemodialysis or peritoneal dialysis. Thirty-two (32) patients (age 5 to 18 years) were enrolled in this 3-week study, with 8 patients (6 given Rapamune and 2 given placebo) in each dose group.

Adverse events were present in all dose and age groups, but there was no dose-limiting toxicity. The most frequently observed adverse event was headache (4 patients). No deaths or serious adverse events were reported and no patient withdrew from the study because of an adverse event. Three (3) patients had vital sign abnormalities reported as adverse events (1 patient with hypertension and 2 patients with hypotension).

9 RISK/BENEFIT SUMMARY AND CONCLUSION

Rapamune (2 mg/day and 5 mg/day), administered in combination with CsA and corticosteroids to primary renal allograft recipients, has been shown to be effective in decreasing the rate of efficacy failure and acute rejection, lowering the need for anti-T lymphocyte antibody therapies to treat rejection, and altering the distribution of the histological severity toward milder acute rejection episodes. These benefits were achieved while maintaining excellent one-year patient and graft survival rates. The safety profile of Rapamune has been well-characterized in 2668 subjects who received Rapamune, 976 of whom were renal transplant patients who received Rapamune at intended doses of 2 mg/day or higher in the phase III studies. Elevations of serum lipid and creatinine levels and decreases in platelet and white blood cell counts occurred more frequently in Rapamune-treated patients than in the control groups. The laboratory and clinical adverse events were manageable with Rapamune dose reduction or discontinuation, with or without the use of countermeasure drug therapy.

For the majority of patients, the Rapamune 2 mg/day dose offers the most favorable benefit/risk ratio. This dose was shown to significantly decrease the incidence efficacy failure and the rate of acute rejection, lower the need for anti-T-lymphocyte antibody therapies to treat rejection, and alter the distribution of the histologic severity toward milder acute rejection episodes. The safety profile of the Rapamune 2 mg/day dose was similar to that of the control therapies: 1) the frequency of adverse effects was similar in these groups with the exceptions of hypercholesteremia, hyperlipemia, lymphocele, tachycardia, epistaxis, acne, and rash, which were reported more frequently in the Rapamune 2 mg/day group. Elevations of cholesterol and triglyceride values were of the most concern but were safely managed with dose-reduction and/or drug therapy and did not result in serious clinical sequelae; 2) rates of discontinuation from therapy for adverse events were similar among the Rapamune 2 mg/day and the control groups; and 3) requirement of dose-reduction was no different in the Rapamune 2 mg/day group compared with control groups.

Rapamune appears to have a distinct safety profile compared with that of the other approved immunosuppressive agents. This difference can be observed when reviewing the categories of the most frequent adverse events and the severity of the events. Manageable elevations of serum lipids are the most noticeable adverse events, followed by decreases in platelet and white blood cell counts. Each is manageable with standard countermeasure therapy. There were no life-threatening, frequently occurring reports of glucose metabolism abnormalities, central nervous system events, or

severe hematologic events. In addition, unlike the calcineurin inhibitors, drug level monitoring is not essential when treating these patients with Rapamune 2 mg/day.

The Rapamune 5 mg/day dose, administered with CsA and corticosteroids, was also shown to be effective in reducing the rate of efficacy failure and preventing acute rejection in renal transplant patients while maintaining excellent one year patient and graft survival. Although the safety profile of this higher dose is acceptable, there was an increased frequency and severity of many dose-related adverse events that resulted in an approximately 2-fold higher rate of discontinuations due to adverse events in the Rapamune 5 mg/day group compared to the Rapamune 2 mg/day, azathioprine or placebo groups. There was no single adverse event that accounted for the majority of discontinuations in the Rapamune 5 mg/day dose group.

High risk patients (black patients, highly HLA mismatched patients, and patients with second transplants) are a special concern, as these patients have poorer outcomes which correspond to higher rates of allograft rejection and chronic graft loss. Study 301 was designed to stratify by race (black vs non-black) in an effort to evaluate the potential activity of Rapamune in this high risk group.

In study 301, higher daily doses of CsA were administered to black patients to achieve CsA trough levels comparable to those in non-black patients. Corticosteroid doses and Rapamune exposure were comparable in black and non-black patients. Rates of efficacy failure were numerically lower in black patients who received Rapamune 5 mg/day than in black patients who received Rapamune 2 mg/day, azathioprine, or placebo. Similar rates of efficacy failure were observed in black patients who received Rapamune 5 mg/day and non-black patients who received Rapamune 2 mg/day, suggesting that Rapamune 5 mg/day may be of benefit in black patients. These results are supported by the pharmacokinetic/pharmacodynamic analysis, in which Rapamune trough levels were shown to have a linear relationship with dose and were unaffected by race. The pharmacodynamic efficacy analysis of race and Rapamune trough concentrations in relation to the probability of acute rejection supports the need for higher doses of Rapamune in black patients to decrease the risk of rejection.

Higher doses of immunosuppressive medications may be associated with the development of opportunistic infection or malignancy. In the phase III trials, no black patients developed PTLD/lymphoma, and few opportunistic infections were reported in black patients receiving Rapamune. In addition, the adverse event profile for black patients was similar to that of all patients. The following adverse events were reported less frequently in black patients receiving Rapamune 5

mg/day than in non-black patients: hypertriglyceridemia, thrombocytopenia, and arthralgia. These data suggest that Rapamune 5 mg/day does not pose an increased risk of over-immunosuppression or toxicity in black patients.

Overall, the Rapamune 5 mg/day dose appears to be well tolerated in black patients. With regard to efficacy failure, this dose also appears to confer a similar level of effectiveness in black patients when compared with the Rapamune 2 mg/day dose in non-black patients. The benefit is most likely related to higher trough concentrations of Rapamune leading to decreased risk of rejection. These results also suggest that, since Rapamune overcomes the immunological resistance in these high risk patients, the drug may have benefit in other groups at high immunologic risk for acute rejection.

In summary, Rapamune (2 mg/day and 5 mg/day) is safe and effective when administered with CsA and corticosteroids; both doses significantly decrease the rate of efficacy failure and incidence of early acute rejection in renal transplant patients while maintaining excellent patient and graft survival. The benefits of the Rapamune 2 mg/day dose for the majority of renal transplant patients and the Rapamune 5 mg/day dose for patients at higher risk for acute rejection clearly outweigh the risks, since the adverse effects of Rapamune are predictable and manageable based on the collective clinical trial experience.

10 REFERENCES

[1] Sehgal SN, Camardo JS, Scarola JA, Maida BT. Rapamycin (Rapamune, rapamune). Curr Opinion Nephrol Hypertension 1995; 4:482-487.

[2] Kahan BD. Rapamune: A new agent for clinical renal transplantation. Transplantation Proc 1997; 29:48-50.

[3] Sollinger HW, et al. Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. Transplantation 1995;60;225-232.

[4] Halloran P, Mathew T, Tomlanovich S, et al. Mycophenolate mofetil in renal allograft recipients: a pooled efficacy analysis of three randomized, double-blind, clinical studies in prevention of rejection. Transplantation 1997;63:39-47.

[5] Nashan B, Moore R, Amlot P, et al. Randomised trial of basiliximab versus placebo for control of acute cellular rejection in renal allograft recipients. Lancet 1997; 350:1193-1198.

[6] Pirsch JD, Miller J, Deierhoi MH, et al. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression after cadaveric renal transplantation. Transplantation 1997;63:977-983.

[7] Valente JF, Hariharan S, Peddi VR, et al. Causes of renal allograft loss in black vs. white transplant recipients in the cyclosporine era. Clin Transplant 1997;11:231-236.

[8] Vincenti F, Kirkman R, Light S, et al. Interleukin-2-receptor blockade with daclizumab to prevent acute rejection in renal transplantation. N Engl J Med 1998;338:161-165.

[9] Cecka JF. Early rejection: determining the fate of renal transplants. Transplant Proc 1991:23 (1 Part 2): 1263-1264.

[10] Gulanikar AC, MacDonald AS, Sungurtekin U, et al. The incidence and impact of early rejection episodes on graft outcome in recipients of first cadaver kidney transplants. Transplantation 1992;53:323-328.

[11] Basadonna GP, Matas AJ, Gillingham KF, et al. Early versus late acute renal allograft rejection; impact on chronic rejection. Transplantation 1993; 55: 993-95.

[12] Lindholm A, Ohlman S, Albrechtsen D, et al. The impact of acute rejection episodes on long-term graft function and outcome in 1347 primary renal transplants created by 3 cyclosporin regimens. Transplantation 1993;56:307-3165.

[13] Cole E, Naimark D, Aprile M, et al. An analysis of predictors of long-term cadaveric renal allograft survival. Clin Transplant 1995; 9:282-288.

[14] Swinnen LJ, Costanzo-Nordin MR, Fisher SG, et al. Increased incidence of lymphoproliferative disorders after immunosuppression with the monoclonal antibody OKT3 in cardiac transplant recipients. N Engl J Med 1990; 323:1723-1728.

[15] Barkholt LM, Dahl H, Enborm M, et al. Epstein-Barr virus DNA in serum after liver transplantation-surveillance of viral activity during treatment with different immunosuppressive agents. Transpl Int 1996; 9:439-445.

[16] Liu J, Farmer JD Jr, Lane WS, Friedman J, Weissman I, Schreiber SL. Calcineurin is a common target of cyclophilin-cyclosporin A and FKBP-FK506 complexes. Cell 1991;66:807-15.

[17] Flanagan WM, Corthesy B, Bram RJ, Crabtree GR. Nuclear association of a T cell transcription factor blocked by FK506 and cyclosporin A. Nature 1992;352:803-7.

[18] Liu J, Albers MW, Wandless TJ, Luan S, Alberg DG, Belshaw PJ, et al. Inhibition of T cell signaling by immunophilin-ligand complexes correlates with loss of calcineurin phosphatase activity. Biochemistry 1992;31:3896-901.

[19] McCaffrey PG, Perrino BA, Soderling TR, Rao A. NF-ATp, a T lymphocyte DNA-binding protein that is a target for calcineurin and immunosuppressive drugs. J Biol Chem 1993 268:3747-52.

[20] Terada N, Lucas JJ, Szepesi A, Franklin RA, Domenico J, Gelfand EW. Rapamycin blocks cell cycle progression of activated T cells prior to events characteristic of the middle to late G_1 phase of the cycle. J Cell Physiol 1993;154:7-15.

[21] Wiederrecht G, Etzkorn F. Immunophilins. Perspect Drug Discov Design 1994;2:57-84.

[22] Galat A, Metcalf SM. Peptidylproline cis/trans isomerases. Prog Biophys Molec Biol 1995;63:67-118.

[23] Fruman D, Klee C, Bierer B, et al. Calcineurin phosphatase in T lymphocytes is inhibited by FK506 and cyclosporine A. Proc Natl Acad Sci USA 1992; 89:3686-3690.

[24] Su Q, Weber L, Le Hir M, et al. Nephrotoxicity of cyclosporin A and FK506: inhibition of calcineurin phosphatase. Ren Physiol Biochem 1995;18:128-139.

[25] Brown EJ, Albers MW, Shin TB, et al. A mammalian protein targeted by G1-arresting rapamycin-receptor complex. Nature 1994; 369:756-761.

[26] Chen Y, Chen H, Rhoad Aã, et al. A putative sirolimus (rapamycin) effector protein. Biochem Biophys Res Comm 1994;203:1-7.

[27] Chiu MI, Katz H, Berlin V. RAPT1, a mammalian homolog of yeast TOR, interacts with the FKBP12/rapamycin complex. Proc Natl Acad Sci *USA* 1994; 91: 12574-8.

[28] Sabatini DM, Erdjument Bromage H, Lui M, et al. RAFT1: a mammalian protein that binds to FKBP12 in a rapamycin-dependent fashion and is homologous to yeast TORs. Cell 1994;78:35-43.

[29] Sabers CJ, Martin MM, Brunn GJ, et al. Isolation of protein target of FKBP12-rapamycin complex in mammalian cells. J Biol Chem 1994; 270:815-822.

[30] Vathsala A, Chou TC, Kahan BD. Analysis of the interactions of immunosuppressive drugs with cyclosporine in inhibiting DNA proliferation. Transplantation 1990;49:463-72.

[31] Kahan BD, Gibbons S, Tejpal N, Chou TC, Stepkowski S. Synergistic effect of the rapamycin-cyclosporin combination median effect analysis of in-vitro immune performances by human T lymphocytes in PHA, CD3, and MLR proliferative and cytotoxic assays. Transplant Proc 1991;23:1090-1.

[32] Kimball PM, Kerman RH, Kahan BD. Production of synergistic but non-identical mechanisms of immunosuppression by rapamycin and cyclosporine. Transplantation 1991;51:486-90.

[33] Stepkowski SM, Tian L, Napoli KL, et al. Synergistic mechanisms by which Rapamune and cyclosporin inhibit rat heart and kidney allograft rejection. Clin Exp Immunol 1997; 108:63-68.

[34] Todo D, Fung JJ, Demetris AJ, Jain A. Venkataramanan R. Starzl TE. Early trials with FK506 as primary treatment in liver transplantation. Transplant Proc 1989;22:13-6.

[35] Fung JJ, Todo S, Jain A, McCauley J. Alessiani M. Scotti C. Conversion from cyclosporine to FK506 in liver allograft recipients with cyclosporine-related complications. Transplant Proc 1990;22:6-12.

[36] Palmer BF, Toto RD. Severe neurologic toxicity induced by cyclosporine in three renal transplant patients. Am J Kidney Dis 1991;18:116-21.

[37] Murgia MG, Jordan S, Kahan BD. The side effect profile of Rapamune: A phase I study in quiescent cyclosporine-prednisone-treated renal transplant patients. Kidney Internat 1996; 49:209-216.

[38]Tricontinental mycophenolate mofetil renal transplantation study group. A blinded, randomized clinical trial of mycophenolate mofetil for the prevention of acute rejection in cadaveric renal transplantation. Transplantation 1996;61:1029-1037.

[39] Mayer A, Dmitrewski J, Squifflet J, Besse T, Grabensee B, Klein B, et al. Multicenter randomized trial comparing tacrolimus (FK506) and cyclosporine in the prevention of renal allograft rejection. Transplantation 1997;64:436-443.

[40]DiJoseph J, Mihatsch M, Sehgal S. Renal effects of rapamycin in the spontaneously hypertensive rat. Transplantation International 1994;7:83-88.

[41]Andoh T, Burdmann E, Franceschini N, Houghton D, Bennett W. Comparison of acute rapamycin nephrotoxicity with cyclosporine and FK506. Kidney International 1996;50:1110-1117.

[42] Bennett W, DeMattos A, Meyer M, Andoh T, Barry J. Chronic cyclosporine nephropathy: the Achilles' heel of immunosuppressive therapy. Kidney International 1996;50:1089-1100.

[43]Forrester K, Gill M, Kim D. Review of immunosuppressive agents in transplantation. US Pharmacist, January 1999, HS 25-34.

[44] Myers B. Cyclosporine nephrotoxicity. Kidney Int 1986;30:964.

[45] Holman M, Gonwa T, Cooper B, Husberg B, Goldstein R, Gibbs J, et al. FK 506 -associated thrombotic thrombocytopenic purpura. Transplantation 1993;55:205-06.

[46]Abramowicz D, Pradier O, Marchant A, Florquin S, De Pauw L, Veerstraeten P, et al. Induction of thromboses within renal grafts by high-dose prophylactic OKT3. Lancet 1992;339:777.

[47] 90-day update to integrated summary of safety, sirolimus NDA 21-083. Update submitted 15 March 1999.

[48] Wiener Y, Nakhleh R, Lee M, Escobar f, Venkat J, Kupin W, et al. Prognostic factors and early resumption of cyclosporin A in renal allograft recipients with thrombotic microangiopathy and hemolytic uremic syndrome. Clin Transplantation 1997;11:157-162.

[49]Lindholm A, Welsh M, Alton C and Kahan BD. Demographic factors influencing cyclosporine pharmacokinetic parameters in patients with uremia: Racial differences in bioavailability. Clin Pharmacol Ther 1992;52:359-71.

[50]Spahn J, Brown E, Covar R, Leung D. Do African Americans display a diminished response to glucocorticoids? J Allergy Clin Immunol January 1999 S62.

[51]Scornick J and Cecka J. Immune responsiveness and renal transplantation. In: Cecka J, Terasaki P, editors. Clinical Transplants. Los Angeles: UCLA Tissue Typing Laboratory, 1997:373-79.

[52]Terasacki PI, Cecka JM, Gjertson DW, Takemota S, Cho YW, Yuge J. Risk rate and long -term kidney transplant survival. In: Cecka J, Terasaki P, editors. Clinical Transplants. Los Angeles: UCLA Tissue Typing Laboratory, 1997:443-58.

[53]Neylan JF. Immunosuppressive therapy in high-risk transplant patients: dose-dependent efficacy of mycophenolate mofetil in African-American renal allograft recipients. U.S. renal transplant mycophenolate mofetil study group. Transplantation 1997;64:1277-82.

11 TABLE OF STUDIES

TABLE OF STUDIES

Protocol No Report No	Study Design	No in Study[a]
1. ADEQUATE AND WELL-CONTROLLED TRIALS IN RENAL ALLOGRAFT RECIPIENTS		
0468E1-301-US GMR-32348	Phase III, randomized, double-blind, double-dummy, parallel, two-part, comparative study comparing 2 dose levels of Rapamune with AZA in combination with corticosteroids and CsA: 6 month efficacy, 1 and 2 year graft and patient survival	719
04681E1-302-AU,CA,EU,US GMR-33147	Phase III, placebo-controlled, double blind study of 2 dose levels of Rapamune in combination with corticosteroids and CsA: 6 month efficacy, 1, 2, and 3 year graft and patient survival	576
2. LONG-TERM STUDIES IN RENAL ALLOGRAFT RECIPIENTS		
Single-Blind Study in Renal Allograft Recipients, Including CsA-Reduction Cohorts		
0468E1-203-CA,EU,US GMR-29107	Phase II, single-blind, placebo-controlled 12 month safety and efficacy study of combinations of Rapamune and CsA plus standard corticosteroid therapy in the prophylaxis of renal allograft rejection	151
0468E1-203-GL GMR-29812	Phase II, single-blind, placebo-controlled 12 to 24 month safety and efficacy study of combinations of Rapamune and CsA plus standard corticosteroid therapy in the prophylaxis of renal allograft rejection	52

TABLE OF STUDIES

Protocol No Report No	Study Design	No in Study[a]

TABLE OF STUDIES

Protocol No Report No	Study Design	No in Study[a]

TABLE OF STUDIES

Protocol No Report No	Study Design	No in Study[a]
	Drug-Drug Interaction Studies	
0468E1-135-EU GMR-33150	Phase I, open-label, SD, three-period, crossover, pharmacokinetic study of the potential interaction between Rapamune 10 mg and diltiazem 120 mg in healthy volunteers	18
0468E1-136-US GMR-31057	Phase I, open-label, SD Rapamune, multiple dose ketoconazole, non-randomized, two-period, drug interaction study of Rapamune 5 mg and ketoconazole 200 mg in healthy volunteers	24
0468E1-138-EU GMR-33151	Phase I, SD Rapamune, multiple-dose acyclovir, open-label, two-period, randomized, crossover, drug interaction study of Rapamune 10 mg and acyclovir 200 mg in healthy volunteers	20
0468E1-140-US GMR-31058	Phase I, open-label, SD, randomized, three-period crossover, drug interaction study of Rapamune 10 mg and glyburide 5 mg in healthy volunteers	24
0468E1-141-US GMR-31059	Phase I, SD, open-label, three-treatment, three-period, three-sequence, randomized, crossover, drug interaction study of Rapamune 10 mg and nifedipine 60 mg in healthy subjects	24
0468E1-142-US GMR-31061	Phase I, open-label, non-randomized, two-period, drug interaction study of a single-dose of Rapamune 10 mg and multiple-doses of digoxin 0.25 mg, in healthy subjects	24
0468E1-154-US GMR-33152	Phase I, open-label, non-randomized, two-period, drug interaction study of multiple-doses Rapamune and multiple-doses of norgestrel/ethinyl estradiol (oral contraceptives) in healthy subjects	24
0468E1-156-US GMR-31332	Phase I, open-label, non-randomized, two-period, drug interaction study of single-dose Rapamune and multiple-doses of rifampin in healthy subjects	16
0468E1-163-US GMR-31330	Phase I, open-label, four-treatment, four-period, four-sequence randomized, crossover, drug interaction study of single-doses of Rapamune and microemulsion CsA in healthy subjects	56

TABLE OF STUDIES

Protocol No Report No	Study Design	No in Study[a]

TABLE OF STUDIES

Protocol No Report No	Study Design	No in Study[a]
	Pediatric Dialysis	
0468E1-147-US GMR-31333	Phase I, randomized, double-blind placebo-controlled sequential study of ascending single oral doses of Rapamune in pediatric patients with stable chronic renal failure receiving hemodialysis or peritoneal dialysis	32
	Compassionate Use	
Summary of Emergency Use	Compassionate use of Rapamune for immunosuppression after transplantation	39

TABLE OF STUDIES

Protocol No Report No	Study Design	No in Study[a]

a: Enrollment as presented in original NDA.

FR = France, GB = Great Britain, US = United States, SW = Sweden; DB = double blind, OL = open label, SB = single blind; CsA, cyclosporine; AZA, azathioprine.